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Weight Gain and Maturity in Fetuses Exposed to Low Levels of Lead

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The relationship between prenatal low-level lead exposure and fetal growth was evaluated in a sample of 4354 pregnancies in which the mean umbilical cord blood lead level was 7.0 μg/dl (SD = 3.3; 10th percentile, 3.4 μg/dl, 90th percentile, 10.9 μg/dl). Higher cord blood lead levels were significantly associated with gestations of slightly longer duration. Comparing infants with cord blood lead levels ≥15 μg/dl to those with levels <5 μg/dl, adjusted risk ratios of 1.5 to 2.5 were observed for low birth weight (<2500 g) and for fetal growth indices that express birth weight as a function of length of gestation (e.g., small-for-gestational age, intrauterine growth retardation). The 95% confidence intervals of these risk ratios included 1, however, precluding rejection of the null hypothesis of no association. We conclude that the risk of adverse fetal growth is not increased at cord blood lead levels <15 μg/dl but that modest increases in risk may be associated with levels ≥15 μg/dl. © 1991 Academic Press, Inc

INTRODUCTION

Reports of reproductive problems attributed to high-dose occupational exposure to lead date back more than a century, with increased exposure associated with elevated rates of infertility, stillbirth, and spontaneous abortion (Hall, 1905; Oliver, 1911; Cantarow and Trumper, 1944; Rom, 1976). Several more recent case studies of women who become lead intoxicated during pregnancy suggest that low birth weight, prematurity, and other expressions of impaired fetal growth and development are frequent sequelae among offspring (Bellinger and Needleman, 1985). Within the last decade, evidence that the lower lead levels more typical of community exposures are associated with diverse adverse health effects in young children (U.S. Agency for Toxic Substances and Disease Registry, 1988) has stimulated concern that low-level *in utero* exposure may adversely affect fetal growth and development.

The evidence linking low-level lead exposure during pregnancy to reproductive problems is mixed. In some cohorts, higher prenatal lead exposures within the "subclinical" range have been linked to reduced duration of gestation (Huel *et al.*, 1981; McMichael *et al.*, 1986; Dietrich *et al.*, 1987; Moore *et al.*, 1982; Savitz *et al.*, 1989; Ward *et al.*, 1987) and lower birth weight (Bornschein *et al.*, 1989, Ward *et al.*, 1987). Other studies have failed to find evidence supporting one or both

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of these associations (Angell and Lavery, 1982; Needleman *et al.*, 1984; McMichael *et al.*, 1986; Ernhart *et al.*, 1986; Graziano, 1989).

In assembling a cohort of children for a study of the association between low-level *in utero* lead exposure and later child development (Bellinger *et al.*, 1987), we collected detailed information about the prenatal lead exposure and birth status of more than 4000 newborns. These data provided an opportunity to assess the extent to which maternal low-level lead exposure is associated with disturbed fetal growth in a large urban, socioeconomically advantaged sample.

METHODS

Cohort. The Brigham and Women's Hospital in Boston serves a mainly middle-class urban population not exposed to lead from industrial sources. In 1979–1981, the lead content of more than 11,000 umbilical cord blood specimens was measured by anodic stripping voltammetry (Rabinowitz and Needleman, 1982). The mean (±SD, range) cord blood lead level was 7.0 μg/dl (±3.3, 0.1–35.1). Information about pregnancy exposures, demographic characteristics, and reproductive history was obtained by interviewing 4354 women within 2 days of delivery. Additional information about the course of the index pregnancy, labor, delivery, and fetal outcome was obtained from review of the obstetric and pediatric records (Linn *et al.*, 1982).

Definitions of outcomes. In these analyses, we focus on the association between umbilical cord blood lead level and two indices of fetal growth: birth weight and length of gestation. Birth weight (in grams) was obtained from the obstetric record. Mean birth weight was 3311.9 g (SD = 594.1). Length of gestation (in weeks) was estimated from a woman's last menstrual period, obtained either by self-report or from obstetrician's notes. Mean length of gestation was 39.7 weeks (SE = 2.3). "Preterm" delivery was defined as delivery prior to the 37th week of pregnancy. An infant was considered "low birth weight" (LBW) if birth weight was less than 2500 g and "small for gestational age" (SGA) if birth weight was below the 10th percentile for infants of the same gestational age within this cohort. "Intrauterine growth retardation" (IUGR) was defined as birth weight more than two standard deviations below the mean for infants of the same gestational age within this cohort.

Analysis. The association between prenatal lead exposure and fetal growth was estimated using multiple linear regression analysis for continuously distributed outcomes and multiple logistic regression analysis for dichotomous outcomes. Adjustment was made for several variables known or presumed to be associated with fetal development (Table 1): maternal age at delivery, marital status (single/married), mother employed at conception (yes/no), maternal education (5–11, 12, 13–15, ≥16 years), race (black/nonblack), maternal ponderal index (defined as weight/height^2), parity (firstborn/later born), smoking status (never, former, stopped during pregnancy, current), beer or wine consumption during pregnancy (any/none), hard liquor consumption during pregnancy (any/none), consumption of three or more cups of coffee per day in the first trimester of pregnancy (yes/no), hematocrit at delivery, maternal diabetes (yes/no), and delivery by caesarian sec-

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[a] Mean (SD).

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TABLE 1
SAMPLE CHARACTERISTICS

Variables	Cord blood lead group (μg/dl)			
	0–4.9	5–9.9	10–14.9	≥15.0
Maternal age at delivery (yr)	27.7 (5.2)*	27.7 (5.4)	27.6 (5.7)	27.6 (6.8)
% Black	12.2	15.7	18.4	23.5
Maternal education (highest grade)				
% 5–11	10.1	14.1	15.5	32.7
% 12	20.5	22.8	25.7	17.8
% 13–16	22.0	22.7	23.1	15.8
% 17+	47.4	40.4	35.7	33.7
Prepregnancy weight (lbs)	128.3 (23.2)	129.8 (23.8)	130.2 (26.7)	133.0 (24.3)
Weight gain during pregnancy (lbs)	29.0 (10.5)	29.0 (10.7)	29.1 (12.2)	26.7 (11.1)
% Unmarried	14.1	17.5	21.8	32.4
% Employed at conception	53.0	56.3	57.2	52.9
Smoking status				
% Never	53.3	44.0	35.7	32.6
% Former	7.1	7.8	6.0	4.2
% Stopped during pregnancy	22.6	22.8	21.2	20.0
% Current	17.1	25.4	37.1	43.2
% Consuming beer/wine during pregnancy	24.7	26.6	30.7	20.6
% Consuming spirits during pregnancy	7.3	9.1	13.0	12.8
% Consuming ≥3 cups of coffee (1st tri)	15.7	21.3	26.6	21.6
% Diabetic	2.6	2.4	1.9	1.0
% Delivery by cesarean section	21.8	22.2	22.4	12.8
Hematocrit at delivery	37.5 (3.1)	37.2 (3.2)	37.1 (3.3)	36.6 (2.7)
% Firstborn	48.6	51.3	56.7	50.5

* Mean (SD).

tion (yes/no). In modeling birthweight, adjustment was made for length of gestation. Complete data on all outcomes and covariates were available for 3503 infants. In the linear regression analyses, the coefficient for cord blood lead level represents the change in an outcome associated with each unit increase in lead level (i.e., each μg/dl). For the logistic regression analyses, the exponentiated coefficient for lead represents the change in risk ratio associated with each unit increase in cord blood lead level. In an additional set of linear and logistic regression analyses, cord blood lead level was expressed as its natural log transform. Because the differences between the results of the two sets of analyses are minimal, only the results of analyses using the measured value of cord blood lead level are presented. In order to examine more closely the form of the dose–effect relationships between fetal lead exposure and continuous measures of fetal outcome, cord blood lead level was also fitted as a set of three indicator variables representing four blood lead ranges: 0–4.9, 5.0–9.9, 10–14.9, and ≥15 μg/dl. For dichotomous fetal outcomes, separate risk ratios were calculated for infants with cord blood lead levels of 5.0–9.9, 10.0–14.9, and ≥15 μg/dl, using infants with levels <5 μg/dl as the reference group.

Analyses were conducted using PC SAS (SAS Institute, Inc., 1985) and STATA (Computing Resource Center, 1989).

RESULTS

In bivariate analyses, birth weights were lower among infants with higher cord blood lead levels, but this association was not significant. Length of gestation, however, was significantly greater among infants with higher cord blood lead levels (Table 2). For neither outcome was the direction of association with cord blood lead level affected by adjustment for all covariates. The adjusted mean birth weight among infants with cord blood lead levels greater than 15 μg/dl was 80–100 g lower than the mean birth weights of infants in the other three groups (Table 3). The adjusted mean length of gestation increased in a dose–effect manner, but with no additional increase apparent once blood lead levels exceeded 10 μg/dl. The mean duration of gestation among infants in the highest cord blood lead group was less than ½ week longer than the mean gestation of infants in the lowest lead group, however (Table 3). The full regression model accounted for 41.3% of the variance in birth weight and 7.8% of the variance in length of gestation.

The percentages of infants meeting the criteria for the three birth weight-based indices of fetal dysmaturity (i.e., LBW, SGA, IUGR) increased in a monotonic manner as cord blood lead level increased (Table 4). For each index, a unit increase in cord blood lead level (1 μg/dl) was associated with a modest increase in the risk of poor outcome. The risk of adverse outcome associated with a 10 μg/dl increase in blood lead level was 1.57, 1.16, and 1.86 for LBW, SGA, and IUGR, respectively. Calculation of separate risk ratios associated with cord blood lead levels of 5.0–9.9, 10.0–14.9, and ≥15 μg/dl indicated that, for all three indices, the risk of poor outcome was generally stable among infants with levels below 15 μg/dl. Among infants with levels above 15 μg/dl, the risk of LBW and IUGR was increased at least twofold and the risk of SGA was increased by 50% (Fig. 1). Although the upper bound of the 95% confidence interval for these risk ratios ranged from 2.85 (SGA) to 9.82 (IUGR), for all three the lower bound was less than 1.0.

The frequency of premature delivery did not vary significantly across cord blood lead categories (Table 4). In fact, cord blood lead levels greater than 5 μg/dl were associated with a reduced risk of premature delivery (Fig. 1).

TABLE 2
MULTIPLE REGRESSION OF FETAL GROWTH OUTCOMES ON CORD BLOOD LEAD LEVEL

	Crude			Adjusted[c]		
Outcome[a]	Coefficient[b]	SE	*P*	Coefficient	SE	*P*
Birth weight[c]	−2.90	2.74	0.29	−3.00	2.41	0.21
Length of gestation	0.03	0.01	0.007	0.04	0.01	0.0002

[a] n = 4345 and 3503 for crude and adjusted birthweight analyses, respectively; n = 4341 and 3503 for crude and adjusted length of gestation analyses, respectively.

[b] Coefficient represents the change in outcome for each unit increase in cord blood lead level (1 μg/dl).

[c] Adjusted for maternal age; marital status; working status; education; race; ponderal index; parity; smoking status; beer, wine, spirit, and coffee consumption during pregnancy; hematocrit at delivery; diabetes; and mode of delivery (see text for bases of categorization).

TABLE 3
INDICES OF FETAL GROWTH FOR INFANTS CLASSIFIED BY CORD BLOOD LEAD LEVEL

Cord blood lead category (μg/dl)	N	Birth weight (g)[a] ($\bar{X}$ ± SE)	Length of gestation[a] (weeks) ($\bar{X}$ ± SE)
<5	948	3319.6 ± 16.0	39.5 ± 0.1
5.0–9.9	2030	3340.9 ± 11.5	39.8 ± 0.1
10.0–14.9	442	3319.1 ± 22.6	39.9 ± 0.1
≥15.0	83	3241.4 ± 50.5	39.9 ± 0.2

[a] Adjusted for maternal age; marital status; employment status; education; race; ponderal index; parity; smoking status; beer, wine, spirit, and coffee consumption during pregnancy; hematocrit at delivery; diabetes; and mode of delivery (see text for bases of categorization). Birth weight also adjusted for length of gestation.

We were unable to identify factors that modify the association between cord blood lead level and fetal growth. Unlike Bornschein *et al.* (1989), we found no evidence that the association between cord blood lead level and birth weight differs according to maternal age. Within each age stratum (<20, 20–29, ≥30 years), mean birth weight was nearly identical among infants with cord blood lead levels in the ranges of 0–5, 5–10, and 10–15, but somewhat lower among children with cord blood lead levels greater than 15 μg/dl.

The association between cord blood lead level and birth weight was also similar among black and nonblack women. In each racial group, infants with cord blood lead levels in the ranges of 0–5, 5–10, and 10–15 had comparable mean birth weights, while infants with cord blood lead levels greater than 15 μg/dl had slightly lower birth weights.

TABLE 4
CORD BLOOD LEAD LEVEL AND INDICES OF FETAL GROWTH AND MATURITY

	Cord blood lead group				Risk ratio[b]	
Outcome[a]	0–4.9	5.0–9.9	10.0–14.9	15.0+	Crude (95% CI)	Adjusted[c] (95% CI)
LBW	7.7%	7.0%	8.4%	9.8%	1.01 (0.98, 1.04)	1.05 (1.00, 1.10)
SGA	9.4%	10.9%	12.3%	17.7%	1.04 (1.01, 1.07)	1.02 (0.98, 1.05)
IUGR	1.5%	2.0%	2.4%	3.9%	1.06 (1.01, 1.12)	1.06 (1.00, 1.13)
Premature	7.8%	6.3%	8.2%	5.9%	0.99 (0.96, 1.03)	0.98 (0.93, 1.02)

[a] Definitions: LBW, birth weight <2500 g; SGA, birth weight <10th percentile for gestational age; IUGR, birth weight >2 SD below mean for gestational age; and premature, length of gestation <37 weeks.

[b] Risk ratio associated with each unit increase in cord blood lead level (1 μg/dl).

[c] Adjusted for maternal age; marital status; working status; education; race; ponderal index; parity; smoking status; beer, wine, spirit, and coffee consumption during pregnancy; hematocrit at delivery; diabetes; and mode of delivery (see text for bases of categorization).

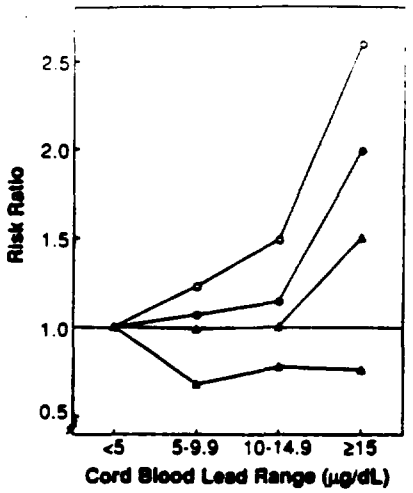

FIG. 1. Risk ratios for four indices of fetal dysmaturity associated with four ranges of cord blood lead levels. The reference group is infants with cord blood lead levels <5 μg/dl. Risk ratios are adjusted for the complete set of covariates listed in text. (○) Intrauterine growth retardation. (●) low birth weight, (△) small-for-gestational age, (▲) premature.

DISCUSSION

In this large sample, fetal growth does not appear to be associated with prenatal lead exposures corresponding to cord blood lead levels in the range of 0 to 15 μg/dl. Among infants with cord blood lead levels of 5.0 to 14.9 μg/dl, the risk ratios for LBW, SGA, and IUGR were 1.0 to 1.5 and may reflect residual confounding.

These data are compatible, however, with an increased prevalence of fetal dysmaturity among infants with cord blood lead levels greater than 15 μg/dl. The association was generally stronger for indices of fetal growth that express birth weight as a function of length of gestation. Among infants with cord blood lead levels >15 μg/dl, the risk of being "small-for-gestational age," "intrauterine growth retarded," or "low birth weight" was 1.5 to 2.5 times greater than the risk among infants with lead levels below 5 μg/dl. Because of the relatively small numbers of infants with levels greater than 15 μg/dl, as well as the low frequencies of the different markers of fetal dysmaturity, for all three markers the 95% confidence interval for lead's coefficient included 1 (indicating no increased risk).

The suggestion that infants with levels greater than 15 μg/dl are at increased risk appears to be consistent with the findings of Bornschein *et al.* (1989), who reported that an increase in the prevalence of low birth weight was not evident until blood lead levels during gestation reached 12–13 μg/dl.

Increased prenatal lead exposure was not associated with a decrease in length of gestation, as reported in several other studies (Moore *et al.*, 1982; McMichael *et al.*, 1986; Dietrich *et al.*, 1987). In fact, higher exposure was associated with significantly longer gestations, a finding not previously reported. The magnitude

of the association is small, approximately a one-half-week difference in the mean lengths of gestation of the least and most highly exposed infants. On the other hand, the increase was dose-related, lending greater credibility to this finding. The high level of statistical significance is attributable largely to the size of our sample.

There are several possible explanations for the inconsistencies among studies in the observed associations between prenatal lead exposure and fetal maturity. One factor is differences in outcome definition. Some investigators treat birth weight as a continuous variable while others simply classify newborns as "low birth weight" or "normal." A second difference among studies is the index of prenatal lead exposure. The biokinetics of lead in the maternal–fetal unit and how they change over the course of pregnancy are not well understood, leading to uncertainty as to the relationships among various indices of *in utero* exposure. Exposure estimates have been based on maternal occupational history, maternal blood lead concentrations during pregnancy, infants' umbilical cord blood lead levels at delivery, placental tissue lead levels, and maternal and newborn hair lead levels. These indices sample different storage compartments of lead and, thus, represent different exposure averaging times. It is likely that they provide complementary, but not necessarily duplicative, information about fetal exposure (Ernhart *et al.*, 1986; Stark and Schell, 1990). The degree of specificity in the associations between the various indices of fetal outcome and the various indices of fetal exposure remains uncertain.

An additional type of explanation for inconsistency in the associations reported involves differences among cohorts in factors that may modify lead's impact on fetal outcome (e.g., ethnicity, socioeconomic status, adequacy of prenatal care). Finally, the cohorts studied differ substantially in size (ranging from <200 to >4000), resulting in differences in power to detect associations between fetal lead exposure and reproductive outcomes of relatively low frequency.

In summary, our findings are generally consistent with the hypothesis that cord blood lead levels greater than 15 μg/dl are associated with a modest increase in risk of *in utero* growth impairment. Levels below 15 μg/dl do not appear to increase an infant's risk.

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LEAD EXPOSURE AND CHILD DEVELOPMENT

An International Assessment

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1.2
Effects of Low-Level Lead Exposure on Paediatric Neurobehavioural Development: Current Findings and Future Directions

L. D. GRANT and J. M. DAVIS

INTRODUCTION

The topic addressed at this Edinburgh Workshop, i.e., relationships between lead (Pb) exposure and neurobehavioural development effects in children, has been one of widespread interest and debate for many years. It has been of especially keen interest and importance in nations where extensive exposure of the general population (including paediatric segments) occurs as the result of mining, smelting, manufacturing processes, and/or consumer uses of lead or lead products. Toxic effects arising from exposures to lead of either adult or paediatric populations, whether directly or indirectly (secondarily) associated with occupational/workplace contamination or via various environmental pathways (e.g., air, water, soil, dust, food, etc.) have been a public health matter of longstanding concern to governmental bodies at the Federal, State, and local levels in the United States and at analogous governmental levels in many other nations as well.

The development of sound regulatory policies aimed at providing adequate public health protection against the toxic effects of lead is highly dependent upon the extent and quality of the scientific knowledge concerning sources, routes, and levels of the lead exposure for various population segments and the biological relationships involved in the uptake, distribution, retention, and consequent health effects of the metal or its compounds. Studies concerning the effects of lead exposure early in development on the physical and neurobehavioural development of children form an extremely important part of the scientific data base currently being drawn upon in the development of

regulatory policies for the control of lead exposure in the United States and elsewhere, including the United Kingdom, Canada, Australia, and various European countries.

The effects of early lead exposure on neurobehavioural and physical development of children are among numerous types of health effects evaluated as part of recent assessments of scientific bases for policy decisions by the United States Environmental Protection Agency (US EPA) concerning regulatory actions aimed at control of human lead exposure via the ambient air or water and/or due to more specific sources, e.g., the combustion of leaded gasoline. The most thorough and comprehensive evaluation of these and other lead health effects is presented in the US EPA document *Air Quality Criteria for Lead* (US EPA, 1986a) and an associated Addendum (US EPA, 1986b).

This paper attempts: (1) to provide a concise overview of the evaluations contained in these two EPA source documents and selected other emerging findings pertinent to the subject of the present meeting; (2) to note some policy considerations arising out of such evaluations; and (3) to highlight certain issues useful in defining future research directions. One major issue focussed on throughout this review is the delineation of exposure–effect (or dose–response) relationships for various types of lead effects on paediatric development, starting with those associated with severe high-level lead intoxication and proceeding to those seen with lesser exposure. Particular emphasis is placed on newly emerging results from ongoing prospective studies conducted by many of the research teams represented at this meeting and on issues that might be profitably investigated as part of their future research efforts.

OVERT LEAD INTOXICATION IN CHILDREN

The most serious outcomes of severe lead intoxication, encephalopathy and the associated high risk of death, have long been of much concern and study. Symptoms of encephalopathy similar to those that occur in adults have been reported in infants and young children (Oliver, 1911; Blackfan, 1917; McKhann and Vogt, 1926; Cumings, 1959; Chisolm, 1968), with much higher incidence of severe encephalopathic symptoms and deaths among them than in adults. This may reflect the greater difficulty in recognizing early symptoms in young children, thereby allowing intoxication to proceed to a more severe level before treatment is initiated (Lin-Fu, 1972). In regard to the risk of death in children, the mortality rate for encephalopathy cases was approximately 65% prior to the introduction of chelation therapy as standard medical practice (Greengard *et al.*, 1965; National Academy of Sciences, 1972). The following mortality rates have been reported for children experiencing lead encephalopathy since the inception of chelation therapy as the standard treatment approach: 39% (Ennis and Harrison, 1950); 20–30% (Agerty, 1952); 24% (Mellins and Jenkins, 1955); 18% (Tanis, 1955); and 5% (Lewis *et al.*, 1955). These data, and those tabulated more recently (National Academy of Sciences, 1972), indicate that once lead poisoning has progressed to the point of

encephalopathy, a life-treatening situation clearly exists and, even with medical intervention, is apt to result in a fatal outcome.

Determining precise values for lead exposures necessary to produce acute symptoms, such as lethargy, vomiting, irritability, loss of appetite, dizziness, etc., or later neurotoxic sequelae in humans, is difficult in view of the paucity of data on environmental lead exposure levels, period(s) of exposure, or body burdens of lead existing prior to manifestation of symptoms. Nevertheless, enough information is available to permit reasonable estimates to be made regarding the range of blood lead (PbB) levels associated with acute encephalopathic symptoms or death. Available data indicate that lower PbB levels among children than among adults are associated with acute encephalopathy symptoms. The most extensive compilation of information on a paediatric population is a summarization (National Academy of Sciences, 1972) of data from Chisolm (1962, 1965) and Chisolm and Harrison (1956). This data compilation relates occurrence of acute encephalopathy and death in children in Baltimore to PbB levels determined by the Baltimore City Health Department between 1930 and 1970. Blood lead levels formerly regarded as 'asymptomatic' and other signs of acute lead poisoning were also tabulated. Increased lead absorption in the absence of detected symptoms was observed at PbB levels ranging from 60 to 300 μg/dl (mean = 105 μg/dl). Acute lead poisoning symptoms other than signs of encephalopathy occurred from 60 to 450 μg/dl (mean = 178 μg/dl). Signs of encephalopathy (hyperirritability, ataxia, convulsions, stupor, and coma) were associated with PbB levels of 90 to 800 μg/dl (mean = 330 μg/dl). The distribution of PbB levels associated with death (mean = 327 μg/dl) was essentially the same as for levels yielding encephalopathy. These data suggest that PbB levels capable of producing death in children are essentially identical to those associated with acute encephalopathy and that such effects are usually manifested in children starting at approximately 100 μg/dl. Certain other evidence from scattered medical reports (Gant, 1938; Smith *et al.*, 1938; Bradley *et al.*, 1956; Bradley and Baumgartner, 1958; Cumings, 1959; Rummo *et al.*, 1979), however, suggests that acute encephalopathy in the most highly susceptible children may be associated with PbB levels of 80 to 100 μg/dl (see US EPA, 1977).

Central nervous system (CNS) pathology findings vary in cases of fatal lead encephalopathy among children (Blackman, 1937; Pentschew, 1965; Popoff *et al.*, 1963) and often include cerebral oedema, altered capillaries (endothelial hypertrophy and hyperplasia), and perivascular glial proliferation. Neuronal damage is variable and may be caused by anoxia. However, in some cases gross and microscopic changes are minimal (Pentschew, 1965). More detailed information on encephalopathic brain changes has been gained by studying animal models. Studies of lead intoxication in the CNS of developing rats have shown vasculopathic changes (Pentschew and Garro, 1966), reduced cerebral cortical thickness and reduced number of synapses per neuron (Krigman *et al.*, 1974a), and reduced cerebral axonal size (Krigman *et al.*, 1974b). Biochemical changes in the CNS of lead-treated neonatal rats have also demonstrated reduced brain lipid content but no alterations of neural lipid composition (Krigman *et al.*, 1974a) and a reduced cerebellar DNA

content (Michaelson, 1973). In cases of lower-level lead exposure, subjectively recognizable neuropathological features may not occur (Krigman, 1978). Instead there may be subtle changes at the level of the synapse (Silbergeld *et al.*, 1980) or dendritic field, myelin–axon relations, and organization of synaptic patterns (Krigman, 1978). Since the nervous system is a dynamic structure rather than a static one, it undergoes compensatory changes (Norton and Culver, 1977), maturation and aging (Sotelo and Palay, 1971), and structural changes in response to environmental stimuli (Coss and Globus, 1978). Thus, whereas massive structural damage in many cases of acute encephalopathy would be expected to cause lasting neurotoxic sequelae, some other CNS effects due to severe early lead insult might be reversible or compensated for, depending upon age and duration of toxic exposure. This raises the question of whether effects of early overt lead intoxication are reversible beyond the initial intoxication or continue to persist.

In cases of severe non-fatal episodes of lead encephalopathy, the neurological sequelae that occur are qualitatively similar to those often seen after traumatic or infectious cerebral injury, with permanent sequelae being more common in children than in adults. The most severe paediatric sequelae are cortical atrophy, hydrocephalus, convulsive seizures, and severe mental retardation (Mellins and Jenkins, 1955; Perlstein and Attala, 1966; Chisolm, 1968). Children who recover from acute lead encephalopathy but are re-exposed to lead almost invariably show evidence of permanent CNS damage (Chisolm and Harrison, 1956). Even if further lead exposure is minimized, 25 to 50% show severe permanent sequelae, such as seizure disorders, blindness, and hemiparesis (Chisolm and Barltrop, 1979).

Lasting neurotoxic sequelae of overt lead intoxication in children in the absence of acute encephalopathy have also been reported. Byers and Lord (1943) reported that children with previous lead poisoning later made unsatisfactory progress in school. Sensorimotor deficits, short attention span, and behavioural disorders have been confirmed in children with known high lead exposures but without a history of life-threatening forms of acute encephalopathy (Chisolm and Harrison, 1956; Cohen and Ahrens, 1959; Kline, 1960). Perlstein and Attala (1966) also reported neurological sequelae in 140 of 386 children (37%) following lead poisoning without encephalopathy. Such sequelae included mental retardation, seizures, cerebral palsy, optic atrophy, and visual–perceptual problems in some children with minimal intellectual impairment. Numerous studies (Cohen *et al.*, 1976; Fejerman *et al.*, 1973; Pueschel *et al.*, 1972; Sachs *et al.*, 1978, 1979, 1982) suggest that, in the absence of encephalopathy, chelation therapy may ameliorate the persistence of neurotoxic effects of overt lead poisoning (especially cognitive, perceptual, and behavioural deficits). On the other hand, another study found a residual effect on fine motor performance even after chelation (Kirkconnell and Hicks, 1980).

In summary, pertinent literature demonstrates that lead poisoning with encephalopathy results in a greatly increased incidence of permanent neurological and cognitive impairments. Also, several studies showed that children with overt, symptomatic lead intoxication in the absence of encephalopathy experience persisting neurological and behavioural impairments.

NON-OVERT LEAD INTOXICATION IN CHILDREN

Besides neurotoxic effects associated with overt lead intoxication in children, much evidence indicates that lead exposures not leading to overt paediatric lead intoxication can induce neurological dysfunctions. This issue has attracted much attention and controversy during the past 10 to 20 years. The evidence concerning occurrence of significant neurotoxic deficits at relatively low lead exposure levels is quite mixed and interpretable only after a thorough critical evaluation of methods employed in the various important studies (see chapter by Smith on methodological issues, this volume). Based on five criteria (adequate markers of exposure to lead, sensitive measures, appropriate subject selection, control of confounding covariates, and appropriate statistical analysis), the population studies summarized in Table 1 were conducted rigorously enough to warrant review in the EPA Criteria Document (US EPA, 1986a). Even so, no epidemiological study is completely flawless and, therefore, overall interpretation of such findings must be based on evaluation of the following: (1) the internal consistency and quality of each study; (2) the consistency of results obtained across independently conducted studies; and (3) the plausibility of results in view of other available information.

Rutter (1980) classified studies evaluating neurobehavioural effects of lead exposure in non-overtly lead intoxicated children according to several types, including four categories reviewed below: (1) clinic-type studies of children thought to be at risk because of high lead levels; (2) other studies of children drawn from general (typically urban or suburban) paediatric populations; (3) samples of children living more specifically in close proximity to lead-emitting smelters; and (4) studies of mentally retarded or behaviourally deviant children. Major attention is accorded here to studies falling under the second and third categories. A final section discusses some initial results beginning to emerge from long-term prospective studies, which relate effects on early neuropsychological development and later neuropsychological functioning to lead exposure histories for children documented back to birth or prenatally.

Clinic-type studies of children with high lead levels

Clinic-type studies are typified by evaluation of children with high lead body burdens as identified through lead screening programmes or other large-scale programmes focussing on mother–infant health relationships and early childhood development. The key features and most salient results emerging from such studies are summarized in Table 1. Comments on important points concerning such studies follow.

De la Burde and Choate (1972) found neurological dysfunctions, fine motor dysfunction, impaired concept formation, and altered behavioural profiles in 70 Richmond, VA preschool children exhibiting pica and elevated PbB levels (all $> 30\,\mu g/dl$; mean $= 59\,\mu g/dl$) compared to matched non-pica control subjects. All mothers were followed during pregnancy, and the children were postnatally evaluated by regular paediatric neurological examinations, psychological testing, and medical interviews. Children subject to prenatal,

Table 1 Summary of studies on neurobehavioural functions of lead-exposed children[a]

Reference	Population studied	N/group	Age at testing, year (range)	Mean blood lead, µg/dl (range or S.D.)	Psychometric tests employed	Summary of results				Levels of significance[b]
Clinic-type studies of children with high lead levels										
							C	Pb		
de la Burde and Choate (1972)	Inner city (Richmond, VA)	C = 72 Pb = 70	4.0 4.0	?[c] 58 (30–100)[d]	IQ (Stanford–Binet)	Score:	94	89		
						% subnormal[e]	10	25		< 0.05
					Fine motor		26	45		< 0.05
					Gross motor		7	16		N.S.
					Concept formation		10	15		N.S.
					Behaviour profile		10	30		< 0.01
de la Burde and Choate (1975)	Follow-up same subjects	C = 67 Pb = 70	7–8 7–8	PbT: 112 µg/g 202 µg/g	WISC Full Scale	Score:	90	87		
					IQ	% subnormal[e]	6	24		0.01
					Verbal IQ		9	18		N.S.
					Performance IQ		13	24		N.S.
					Bender Gestalt		27	49		0.01
					Reading		7	12		N.S.
					Spelling		11	16		N.S.
					Arithmetic		7	12		N.S.
					Goodenough–Harris draw test		1	13		0.02
					Auditory vocal assoc.		13	31		0.01
					Tactile recognition		3	15		0.05
					Behaviour profile		3	25		0.001
Rummo (1974); Rummo *et al.* (1979)	Inner city (Providence, RI)	C = 45 Pb_1 = 15 Pb_2 = 20 Pb_3 = 10	5.8 5.6 (4–8) 5.6 (4–8) 5.3	23 (8) 61 (7) 68 (13) 88 (41)	McCarthy Scales:	C	Pb_1	Pb_2	Pb_3	
					Gen. cognitive	93	94	88	77	< 0.01
					Verbal	46	46	44	37	< 0.05
					Perceptual	48	49	46	38	< 0.05
					Quantitative	45	44	41	35	< 0.01
					Memory	47	46	43	36	< 0.01
					Motor	52	52	50	40	< 0.01
					Parent ratings	8	10	10	18	< 0.01
					Neurological exam	7/12 measures sig. different				

continued

Table 1 *continued*

Reference	Population studied	N/group	Age at testing, year (range)	Mean blood lead, µg/dl (range or S.D.)	Psychometric tests employed	Summary of results			Levels of significance[b]
Kotok (1972)	Inner city (New Haven, CT)	C = 25 Pb = 24	2.7 (1.1–5.5) 2.8 (1.0–5.8)	38 (20–55) 81 (58–137)	Denver Developmental:	*Norm*	*C*	*Pb*	
					Gross motor	1.00	1.02	1.06	N.S.
					Fine motor	1.00[f]	0.82	0.81[f]	< 0.01[f]
					Language	1.00[f]	0.82	0.73[f]	< 0.01[f]
Kotok *et al.* (1977)	Inner city (Rochester, NY)	C = 36 Pb = 31	3.6 (1.9–5.6) 3.6 (1.7–5.4)	28 (11–40) 80 (61–200)	IQ Equivalent:	*C*		*Pb*	
					Social	126		124	> 0.10
					Spatial	101		92	< 0.10
					Spoken vocal	93		92	> 0.10
					Info–comprehension	96		94	> 0.10
					Visual attention	93		90	> 0.10
					Auditory memory	100		93	> 0.10
Perino and Ernhart (1974)[f]	Inner city (New York, NY)	Low Pb = 50 Mod. Pb = 30	3–6 3–6	(10–30) (40–70)	McCarthy Scales:	*Low*		*Mod.*	
					Gen. cognitive	90		80	< 0.01
					Verbal	44		39	< 0.05
					Perceptual	44		37	< 0.05
					Quantitative	48		44	N.S.
					Memory	45		42	N.S.
					Motor	46		42	N.S.
Ernhart *et al.* (1981)[f]	Follow-up same subjects	Low Pb = 31 Mod. Pb = 32	8–13	21 (4)[g] 32 (5)	McCarthy Scales:	*Low*		*Mod.*	
					Gen. cognitive	94		82	< 0.05
					Verbal	48		41	< 0.05
					Perceptual	43		40	N.S.
					Quantitative	43		38	N.S.
					Memory	44		39	N.S.
					Motor	49		46	< 0.05
					Reading tests	Not reported			N.S.
					Conners teacher ratings	Not reported			N.S.
					Various experimental tests	Not reported			N.S.

continued

Table 1 *continued*

Reference	Population studied	N/group	Age at testing, year (range)	Mean blood lead, μg/dl (range or S.D.)	Psychometric tests employed	Summary of results				Levels of significance[a]
General population studies										
						C		*Pb*		
Needleman *et al.*	Urban (Boston, MA)	C = 100 Pb = 58	7 7	PbT: < 10 ppm[f] > 20 ppm	WISC Full Scale IQ Verbal IQ Performance IQ Seashore Rhythm Test Token Test Sentence Repetition Test Delayed Reaction Time Teacher Ratings	106.6 103.9 108.7 21.6 24.8 12.6 C > Pb on 3/4 blocks 9.5		102.1 99.3 104.9 19.4 23.6 11.3 8.2		0.03 0.06 0.12 0.002 0.09 0.04 <0.01 0.02
McBride *et al.* (1982)	Urban/suburban (Sydney, Australia)	Low Pb = > 100 Mod. Pb = > 100	4/5 4/5	(2–9) (19–29)	Peabody Picture Vocab. Test Fine Motor Tracking Pegboard Tapping Test Beam Walk Standing Balance Rutter Activity Scale	*Low* ~105 C > Pb 1/4 comparisons ~20 ~30 ~5 C > Pb 1/4 comparisons ~1.9		*Mod.* ~104 ~20 ~31 ~4 ~2.1		N.S. <0.05 N.S. N.S. N.S. <0.05 N.S.
Yule *et al.* (1981)	Urban (London, England)	Group 1 = 34 Group 2 = 48 Group 3 = 49 Group 4 = 35	9 9 8 (6–12) 8	8.8[f] (7–10) 11.6 (11–12) 14.5 (13–16) 19.6 (17–32)	WISC-R Full Scale IQ Verbal IQ Performance IQ Vernon Spelling Test Vernon Math Test Neale Reading Accuracy[b] Neale Reading Compre.[b]	103 101 106 104 97 121 117	103 101 103 98 97 110 110	96 95 98 92 95 96 95	96 94 99 89 95 89 88	0.027 0.043 0.102 0.001 N.S. 0.001 0.001
Yule *et al.* (1984)	Same subjects in Yule *et al.* (1981)	Same	Same	Same	Needleman Teacher Ratings Conners Teacher Ratings Rutter Teacher Ratings, including "Overactivity" factor	1.53 (4/11 items sig. different) 0.26 (3/4 factors sig. at $p < 0.05$) (2/26 items sig. at $p \leqq 0.05$) (5/26 items differ at $0.05 < p < 0.10$) 6%	1.54	2.45 0.37 20%	2.63 17%	0.096 0.04 0.04

Table 1 *continued*

Reference	Population studied	N/group	Age at testing, year (range)	Mean blood lead, μg/dl (range or S.D.)	Psychometric tests employed	Summary of results			Levels of significance[a]
						Low		*High*	
Lansdown *et al.* (1986)	Urban (London, England)	Low = 80 High = 82	9 9	7–12 13–24	WISC-R Full Scale Verbal IQ Performance IQ Neale Reading Accuracy Neale Reading Comprehension Vernon Spelling Vernon Math	107 104 108 115 113 101 100		105 103 106 112 109 99 99	N.S. N.S. N.S. N.S. N.S. N.S. N.S.
						Low	*Med*	*High*	
Smith *et al.* (1983)	Urban (London, England)	High = 155 Med = 103 Low = 145	6.7 6.7 6.7	PbT ≥ 8.0 PbT = 5–5.5 PbT < 2.5 (All in μg/g) $\bar{X}$ PbB = 13.1 μg/dl	WISC-R Full Scale Verbal IQ Performance IQ Word Reading Test Seashore Rhythm Test Visual Sequential Memory Sentence Memory Shape Copying Mathematics Mean Visual RT (seconds) Conners Teacher Ratings	107 105 108 45 21 20 9 14 16 0.37 11	105 103 106 42 20 19 9 14 15 0.37 11	105 103 106 40 20 20 9 14 15 0.39 13	N.S. N.S. N.S. N.S. N.S. N.S. N.S. N.S. N.S. N.S. N.S.
Harvey *et al.* (1983, 1984)	Urban (Birmingham, England)	189	2.5	15.5 (6–30)	British Ability Scales Naming Recall Comprehension Recognition IQ Standford–Binet Items Shapes Blocks Beads Playroom Activity	*Regression F ratio*[f] <1 1.26 <1 <1 <1 <1 2.34 2.46 7			N.S. N.S. N.S. N.S. N.S. N.S. N.S. N.S. N.S. N.S.

continued

Table 1 *continued*

Reference	Population studied	N/group	Age at testing, year (range)	Mean blood lead, µg/dl (range or S.D.)	Psychometric tests employed	Summary of results		Levels of significance[b]
Silva *et al.* (1986b)	Urban (Dunedin, New Zealand	579	11	11.1 (4–50)	WISC-R Full Scale IQ	$r = -0.06$		N.S.
					Performance IQ	$= -0.03$		N.S.
					Verbal	$= -0.05$		N.S.
					Rutter Behavior Rating	R^2	*Incrs. by Pb*	
					Parent	0.21	1.38	0.003
					Teacher	0.10	1.23	0.008
					Inattention Rating			
					Parent	0.24	0.26	N.S.
					Teacher	0.25	1.51	0.001
					Hyperactivity Rating			
					Parent	0.12	1.01	0.015
					Teacher	0.12	0.82	0.028
					Burt Reading Test	0.43	0.28	N.S.
Schroeder *et al.* (1985)	Rural/urban (Wake County, North Carolina)	104	< 2.5 or > 2.5 (0.8–6.5)	6–59	Bayley MDI or Stanford–Binet	Regression analysis of sources for IQ effect:		
						Lead: $F = 7.689$		< 0.01
						SES: $F = 20.159$		< 0.001
	Follow-up same subjects	50	6–12	≦30	Stanford–Binet	Lead: $F < 1$		N.S.
Schroeder and Hawk (1987)	Rural/urban (Lenoir and Hanover Counties, North Carolina)	75	2	21 (6–47)	Stanford–Binet	Regression analysis of IQ against:		
						Current PbB: $F = 12.31$		< 0.0008
						Max. PbB: $F = 10.55$		< 0.0018
						Mean PbB: $F = 10.08$		< 0.002
Smelter area studies						*C*	*Pb*	
Landrigan *et al.* (1975)	Smelter area (El Paso, TX)	C = 78 Pb = 46	9.3 8.3 (3.8–15.9)	< 40 40–68	WISC Full Scale IQ[m]	93	89	N.S.
					WPPSI Full Scale IQ[n]	91	86	N.S.
					WISC + WPPSI Combined	93	88	N.S.
					WISC + WPPSI Subscales	C > Pb on 13/14 scales		
						7/14 scales sig. different		< 0.05
					Neurological testing	C > Pb on 7/8 tests		
						1/8 tests sig. different		< 0.01

continued

Table 1 *continued*

Reference	Population studied	N/group	Age at testing, year (range)	Mean blood lead, µg dl (range or S.D.)	Psychometric tests employed	Summary of results		Levels of significance[b]
McNeil and Ptasnik (1975)	Smelter area (El Paso, TX)	C = 37 Pb = 101	9 9 (1.8–18)	29 (14–39) 58 (40–93)	McCarthy General Cognitive	*C* 82	*Pb* 81	N.S.
					WISC-WAIS Full Scale IQ	89	87	N.S.
					Oseretsky Motor Level	101	97	N.S.
					California Personality	C > Pb, 6/10 items		< 0.05
					Frostig Perceptual Quotient	100	103	N.S.
					Finger–Thumb Apposition	27	29	N.S.
						Mod.	*High*	
Ratcliffe (1977)	Smelter area (Manchester, England	Mod. Pb = 23 High Pb = 24	4.7 (4.1–5.6) 4.8 (4.2–5.4)	28 (18–35) 44 (36–64)	Griffiths Mental Dev.	108	102	N.S.
					Frostig Visual Perception	14.3	11.8	N.S.
					Pegboard Test			
					Dominant hand	17.5	17.3	N.S.
					Nondominant hand	19.5	19.8	N.S.
						C	*Pb*	
Winneke *et al.* (1982)	Smelter area (Duisberg, FRG)	C = 26 Pb = 26	8 8	PbT = 2.4 ppm[h] PbT = 9.2 ppm No PbB	German WISC Full Scale	122	117	N.S.
					Verbal IQ	130	124	N.S.
					Performance IQ	130	123	N.S.
					Bender Gestalt Test	17.2	19.6	< 0.05
					Standard Neurological Tests	2.7	7.2	N.S.
					Conners Teacher Ratings	?	?	N.S.
Winneke *et al.* (1983)	Smelter area (Stolburg, FRG)	89	9.4	PbT: 6.1 to ppm[h] PbB: 14.3 µg/dl	German WISC	% Variance due to PbT		
					Full Scale IQ	−0.0		N.S.
					Verbal IQ	−0.5		N.S.
					Performance IQ	+0.6		N.S.
					Bender Gestalt Test	+2.1		< 0.05
					Standard Neurological Tests	+1.2		N.S.
					Conners Teacher Ratings	0.4–1.3		N.S.
					Wiener Reaction Performance	+2.0		N.S.

continued

Table 1 *continued*

Reference	*Population studied*	*N/group*	*Age at testing, year (range)*	*Mean blood lead, μg/dl (range or S.D.)*	*Psychometric tests employed*	*Summary of results*	*Levels of significance*
Winneke *et al.* (1984)	Smelter area (Nordenham, FRG)	122	6.5	8.2 (4.4–22.8)	German WISC	% Variance due to Pb	
					Short form	−0.3	N.S.
					Verbal IQ	+0.3	N.S.
					Performance	−2.4	N.S.
					Bender Gestalt Test	+0.5	N.S.
					Signalled Reaction Time		
					Short	+0.1	N.S.
					Long	−0.2	N.S.
					Wiener Reaction Time		
					Easy	+4.3	<0.05
					Difficult	+11.0	<0.01

[a]Abbreviations: C = control subjects; Pb = lead-exposed subjects; MDI = mental development index; N.S. = nonsignificant ($p > 0.05$); PbT = tooth lead; WISC = Wechsler Intelligence Scale for Children; WPPSI = Wechsler Preschool and Primary Scale of Intelligence; RT = reaction time
[b]Significance levels are those found after partialling out confounding covariates
[c]Urinary coproporphyrin levels were not elevated
[d]Some with positive radiological findings, suggesting earlier exposure in excess of 40–60 μg/dl
[e]Percentage of each group scoring 'borderline', 'suspect', 'defective', or 'abnormal'
[f]Reanalysis of data by Emhart correcting for methodological problems in earlier published analyses described here mainly did not substantiate significant differences between control and lead-exposed children indicated in last two columns to the right (see chapter text)
[g]Dentine levels not reported for statistical reasons
[h]Reanalyses of Needleman data correcting for methodological problems in earlier published analyses confirmed significant differences between study groups indicated in last two right-hand columns for WISC IQ test result (see chapter text)
[i]Main measure was dentine lead (PbT)
[j]Blood lead levels taken 9–12 months prior to testing; none above 33 μg/dl
[k]Data not corrected for age
[l]This *F* ratio is result of testing the difference in sums of squares for two regression equations (one including and one excluding blood lead levels as an independent variable) against the residual mean square of the equation including blood lead
[m]Used for children over 5 years of age
[n]Used for children under 6 years of age
Source: US EPA (1986)

perinatal, and early postnatal insults were excluded from the study; and all included children had normal neurological examinations and Bayley tests at 8–9 mo of age. Follow-up studies of the same children at 7–8 y (de la Burde and Choate, 1975) revealed continuing CNS impairment in the lead-exposed group. Also, seven times as many lead-exposed children were repeating grades in school or being referred to the school psychologist, despite many of their PbB levels having dropped significantly from at the time of initial study.

In general, the de la Burde and Choate (1972, 1975) studies have many features that argue for the validity of their findings despite shortcomings avoided by many more recent studies. There were appreciable numbers of children (67 lead-exposed and 70 controls) whose PbB values were obtained in preschool years, the psychometric tests employed were well standardized and acceptable as sensitive indicators of neurobehavioural dysfunction, and testing was conducted blind. These studies, on the other hand, can be criticized on several points, although none are sufficient to reject their results. For example, PbB values were not determined for control subjects in the initial study; but the lack of pica history, as well as results of later tooth lead analyses in the follow-up study, render it improbable that lead-exposed subjects were wrongly assigned to the control group. A second problem was use of multiple chi-square statistical tests; but the fact that the control subjects did significantly better on nearly all measures makes it unlikely that all observed effects were due to chance alone. One last problem concerns ambiguities in subject selection which complicate interpretation of the results obtained. Because the lead-exposed group included children with PbB levels of 40 to 100 μg/dl, or of at least 30 μg/dl with "positive radiographic findings of Pb lines in the long bones, metallic deposits in the intestines, or both", observed deficits might best be attributed to PbB levels exceeding 40 μg/dl based on other evidence (Betts *et al.*, 1973) indicating that lead lines are usually seen only if PbB levels exceed 40 to 60 μg/dl.

In another clinic-type study, Rummo (1974) and Rummo *et al.* (1979) found significant neurobehavioural deficits (hyperactivity, lower scores on McCarthy scales of cognitive function, etc.) among Providence, RI inner-city children who had previously experienced high lead exposure that had produced acute lead encephalopathy. Mean maximum PbB levels recorded at the time of encephalopathy were 88 ± 40 μg/dl. However, children with moderate PbB elevation but not manifesting symptoms of encephalopathy did not differ significantly (at $p < 0.05$) from controls on any measure of cognitive functioning, psychomotor performance, or hyperactivity. Still, when data from the Rummo *et al.* (1979) study for performance on the McCarthy General Cognitive Index or several McCarthy Subscales are compared (see Table 1), the scores for long-term moderate-exposure subjects consistently fall below those for control subjects and lie between the latter and the encephalopathy group scores. Thus, long-term moderate lead exposure, in fact, apparently exerted dose-related neurobehavioural effects. The overall dose–response trend may have been shown to be statistically significant by other types of analyses, if larger samples had been assessed, or if control subjects had PbB values <5–10 μg/dl. Note that (1) the maximum PbB levels for the short-

term and long-term exposure subjects were all greater than 40 μg/dl (means = 61 ± 7 and 68 ± 13 μg/dl, respectively), whereas control subjects all had PbB levels below 40 μg/dl (mean = 23 ± 8 μg/dl), and (2) the control and lead-exposed subjects were inner-city children well matched for socioeconomic background, parental education levels, incidence of pica, and other pertinent factors except for parental IQ (not ascertained).

Kotok *et al.* (1977) found a similar pattern of results in a study in which 36 Rochester, NY, control-group children with PbB levels < 40 μg/dl were compared with 31 children with distinctly elevated blood lead levels (61 to 200 μg/dl) but no classical lead intoxication symptoms. Both groups were well matched on important background factors. Again, no clearly statistically significant differences between the two groups were found on numerous tests of cognitive and sensory functions. However, mean scores of control-group children were consistently higher than those of the lead-exposed group for all of the ability classes listed, although the control group children had notably elevated PbB values by current standards. Kotok (1972) had reported earlier that developmental deficiencies (using the Denver Development Screening Test) in a group of children with elevated PbB levels (58 to 137 μg/dl) were identical to those in a control group similar in age, sex, race, environment, neonatal condition, and presence of pica, but with lower PbB levels (20 to 55 μg/dl). The lead-exposed group, however, had PbB levels as high as 137 μg/dl, whereas some control children had levels as high as 55 μg/dl. Thus, the study essentially compared two groups with different degrees of markedly elevated lead exposure and had no true control group.

Perino and Ernhart (1974) reported relationships between neurobehavioural deficits and PbB levels ranging from 40 to 70 μg/dl in a group of 80 inner-city preschool black children, based on the results of a cross-sectional study of children with elevated PbB levels found through the New York City lead screening programme. They reported that the high-lead children had McCarthy Scale IQ scores markedly lower than those of the low-lead group (mean IQ = 80 versus 90, respectively). Also, the normal correlation of 0.52 between parents' intelligence and that of their offspring was found to be reduced to only 0.10 in the lead-exposed group, presumably because of the influence of another factor (lead) that interfered with normal intellectual development of the lead-exposed children. Another possible explanation, however, might be differences in educational backgrounds of parents of control subjects versus lead-exposed subjects, because parental education level was significantly negatively related to PbB levels of children in the study.

Ernhart *et al.* (1981) carried out follow-up evaluations on 63 of the 80 preschool children of the Perino and Ernhart (1974) study once they reached school age, using the McCarthy IQ scales, various reading achievement tests, the Bender–Gestalt test, the Draw-A-Child test, and the Conners Teacher's Questionnaire for hyperactivity. The children's PbB levels were significantly correlated with FEP ($r = 0.51$) and dentine lead levels ($r = 0.43$), but mean PbB levels of the moderately elevated group had decreased after five years. When control variables of sex and parental IQ were extracted by multivariate analyses, observed differences were greatly reduced (albeit still statistically significant) for three of seven tests on the McCarthy scales in relation to

concurrently measured PbB levels but not in relation to earlier PbB levels or dentine lead levels for the same children. This led Ernhart *et al.* (1981) to reinterpret their 1974 (Perino and Ernhart, 1974) IQ results (in which they had not controlled for parental education) as either not likely being due to lead or, if due to lead, then representing only minimal effects on intelligence.

Reanalyses of the data set reported on by Perino and Ernhart (1974) and Ernhart *et al.* (1981) were carried out to correct certain methodological problems associated with the earlier published analyses, as reported by Ernhart (1983, 1984; Ernhart *et al.*, 1985). Reanalysis of relationships between preschool-age children's PbB levels and concurrently obtained McCarthy Scales scores revealed no significant differences (at $p < 0.05$) due to lead; however, lower scores for the higher Pb exposure group on the General Cognitive Index (GCI) did approach significance at $p < 0.09$. Also, reanalysis of relationships between preschool PbB levels and 5-year later school-age outcome variables yielded no indication of persisting lead effects in terms of reading test results or scores on the McCarthy GCI or most of the McCarthy Subscales (except $p = 0.10$ for Verbal Index scores). The reanalysis of school-age PbB levels (newly corrected for haematocrit variation effects) and concurrent reading test and McCarthy Scales scores only found significant differences attributable to lead for lower McCarthy Verbal Index scores ($p < 0.036$ with a 'deviant case' included in the analysis, and $p < 0.07$ with the case excluded). Similar results were found with a different analysis using a 'lead construct index' as a measure of lead exposure that combined preschool- and school-age PbB levels and free erythrocyte protoporphyrin levels. Based on these results, Ernhart *et al.* (1985) concluded that "the reanalyses provide no reasonable support for an interpretation of lead effects in these data". However, they also noted that there was a certain level of unreliability in the measures used and that the sample size limited the power of the statistical analyses. Given such limitations and extensive attention accorded to statistical control of potentially confounding variables in the reanalyses, it is notable that an association between lead and lower Verbal Index scores was still found across several of the analyses (at p values < 0.04 to 0.10) and that an association between preschool-age PbB levels and GCI scores approached significance at $p < 0.09$.

Other investigators (Shapiro and Marecek, 1984; Marecek *et al.*, 1983) studied relationships between lead exposures and psychometric testing outcomes among black children from low socioeconomic status (SES) families in Philadelphia, PA. From among a large target sample of eligible children invited to participate, 199 families enrolled their children. Primary and/or circumpulpal dentine lead levels from shed deciduous teeth (mainly molars) were used to index lead exposure for 188 children (aged 10.6 to 14.7 y; $\bar{X} = 11.8$ y) who underwent neuropsychologic testing. Data on SES and several other potentially confounding variables were obtained for all children and IQ scores for parents of a subset of the children studied. Data analyses (heirarchical multiple regression analyses) first evaluated relationships between dentine lead exposure indices and test scores obtained several years earlier (at age 7 y) on the Bender–Gestalt, Wechsler Intelligence Scale for Children (WISC) subtests, and other tests; other analyses used dentine lead data and

results from concurrently administered psychometric tests. For tests at seven years of age, significant associations were found between dentine lead and performance IQ scores, but not for WISC verbal IQ scores. Similarly, significant relationships (at $p < 0.05$) were found between dentine lead values and concurrently obtained test results for performance abilities on the Bender–Gestalt, WISC, and other tests but not for verbal abilities. This study, while qualitatively suggesting that lead may affect cognitive performance, suffers from several methodological problems, including inadequate control for sampling bias, covarying social factors, and parental IQ, and retrospective estimation of lead exposure at age seven.

Odenbro *et al.* (1983) studied psychological development of children (aged 3 to 6 y) seen in Chicago Department of Health Clinics (August 1976 to February 1977), evaluating scores on the Denver Developmental Screening Test (DDST) and two subtests of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) in relation to PbB levels obtained by repeated sampling during three previous years. A significant correlation ($r = -0.435, p < 0.001$) was found between perceptual visual–motor ability and mean PbB levels. Statistically significant ($p < 0.005$) deficits in verbal productivity and perceptual visual–performance (measured by the WPPSI) were found for groups of children with mean PbB levels of 30 to 40 μg/dl and 40 to 60 μg/dl versus control children with mean PbB levels < 25 μg/dl, using two-tailed Student's *t*-tests; however, significant associations ($p < 0.05$) between PbB levels and developmental retardations in language and fine-motor functions were found only for the 40 to 60 μg/dl group, using the DDST and chi-square analyses. These results suggest neuropsychological deficits associated with PbB levels of 40 to 60 μg/dl in preschool children. However, parental IQs were not measured, and the adequacy of the statistical analyses employed is questionable, especially in regard to lack of use of multivariate analyses that sufficiently control for confounding covariates.

In another study (Molina *et al.*, 1983), high-risk children from families making lead-glazed pottery in a Mexican village were evaluated for lead-associated neuropsychological deficits, using an appropriately adapted Spanish language version of the revised WISC (WISC-R) test and the Bender–Gestalt test. Test results for 33 high-lead children ($\bar{X}$ age: 10 y, 7 mo $\pm$ 2 y, 7 mo) randomly selected from 64 school children with PbB levels > 40 μg/dl ($\bar{X}$: 63.4 $\pm$ 15.8 μg/dl) were compared with those for 30 lower lead children ($\bar{X}$ age: 10 y, 2 mo $\pm$ 2 y, 6 mo) with PbB levels below 40 μg/dl ($\bar{X}$: 26.3 $\pm$ 8.0 μg/dl), using two-tailed Student's *t*-test and the Mann–Whitney *U* test. The high-lead children had significantly lower WISC-R full-scale IQ ($p < 0.01$), verbal IQ ($p < 0.01$), and performance IQ ($p < 0.025$) than did the low-lead control children drawn from among the same low SES families as the high-lead children. A significant negative linear correlation was also observed for the same types of test scores among the high-lead children, but not for such scores among the low-lead children. These results, highly suggestive of lead-related neuropsychological deficits with PbB values > 40 μg/dl, must be viewed with caution in light of failure to include parental IQ levels and lack of adequate multivariate analyses controlling for age, sex, and other factors.

In summary, the above studies generally found that high-risk lead-exposure groups did more poorly on IQ or other types of psychometric tests than referent control groups with lower Pb exposures. Many of the studies did not control for important confounding variables or, when such were taken into account, found that the differences between lead-exposed and control subjects were reduced or were no longer statistically significant. Still, the consistency of finding the lower IQ values and other types of neuropsychological deficits among at-risk higher lead exposure children across most of the studies lend credence to cognitive deficits occurring in apparently asymptomatic children with markedly elevated PbB levels (i.e., starting at 40 to 60 μg/dl and ranging upwards to 70 to 80 μg/dl or higher values).

The magnitude of lead's effects on IQ at the high exposure levels evaluated in these studies is difficult to estimate due to variations in measurement instruments used, variations in adequacy of control for confounding factors, and the fact that many of the referent control groups had what are now recognized to be elevated PbB levels (i.e., averaging in the 20 to 40 μg/dl range). Focussing on estimates of full-scale IQ deficits, Rummo (1974; Rummo *et al.*, 1979) observed a decrement of about 16 IQ points on the McCarthy GCI for postencephalopathic children with PbB values exceeding 80 μg/dl. Asymptomatic children with long-term lead exposures yielding mean PbB values of 68 μg/dl experienced an average 5-point IQ (GCI) decrement, whereas short-term lead-exposed subjects with PbB levels around 60 μgdl showed no decrement compared to controls. The de la Burde subjects, with PbB levels averaging 58 μg/dl, had a mean Stanford–Binet IQ decrement of 5 points upon first testing (de la Burde and Choate, 1975). Ernhart originally reported an average 10-point IQ (GCI) decrement for children with PbB values in the 40 to 70 μg/dl range upon first testing (Perino and Ernhart, 1974) and 12 points upon follow-up 5 years later (Ernhart *et al.*, 1981). However, these reported large decrements were likely due in part to confounding by uncontrolled covariates in the original analyses and, upon reanalysis of the data, are notably reduced. While it could be argued that the Rummo and de la Burde decrements would also be reduced in size if better control for confounding variables were employed, use of control subjects with lower lead exposure (e.g., < 10 μg/dl) would also logically be expected to result in offsetting influences on IQ. Thus, it seems warranted to conclude that the average decrements of about 5 IQ points observed in the de la Burde and Rummo studies represent a reasonable minimal estimate of the magnitude of full-scale IQ decrements associated with notably elevated PbB levels ($\bar{X} \approx 50$ to 70 μg/dl) in asymptomatic children.

General population studies

These studies evaluated samples of non-overtly lead-intoxicated children selected to be representative of general paediatric populations. They focus mainly on asymptomatic children with lower lead body burdens than those of high-risk children in clinic-type studies.

A pioneering general population study by Needleman *et al.* (1979) used

shed deciduous teeth to index lead exposure. Teeth were donated from 70% of 3329 first and second grade children from two towns near Boston. Almost all children who donated teeth (2146) were rated by their teachers on an 11-item classroom behaviour scale used by the authors to assess attention disorders. An apparent dose–response function was reported for ratings on the behaviour scale, not taking potentially confounding variables into account. After excluding various subjects for control reasons, two groups (< 10th and > 90th percentiles of non-circumpulpal dentine lead levels) were provisionally selected for further in-depth neuropsychological testing. Later, some provisionally eligible children were also excluded for various reasons, leaving 100 low-lead (< 10 ppm dentine lead) children for comparison with 58 high-lead (> 20 ppm dentine lead) children. A preliminary analysis on 39 non-lead variables showed significant differences between the low- and high-lead groups for age, maternal IQ and education, maternal age at time of birth, paternal SES, and paternal education. Some of these variables were entered as covariates along with lead into an analysis of covariance. Significant effects ($p < 0.05$) were reported for full-scale WISC-R IQ scores, for WISC-R verbal IQ scores, for 9 of 11 classroom behaviour scale items, and for several experimental measures of perceptual–motor behaviour.

Additional papers published by Needleman and coworkers report on results of the same or further analyses of the data discussed by Needleman *et al.* (1979). For example, a paper by Needleman (1982) provided a summary of findings from the Needleman *et al.* (1979) study, and Burchfiel *et al.* (1980) reported findings concerning EEG patterns for a subset of children from the 1979 study. Needleman (1982) also summarized results of an additional analysis of the 1979 data set, showing a downward shift across the entire cumulative frequency distribution of verbal IQ scores for high-lead subjects. Another paper, by Bellinger and Needleman (1983), provided still further follow-up analyses of the 1979 data set, focussing mainly on comparison of the low- and high-lead children's observed versus expected IQs based on their mother's IQ; regression analyses showed that IQs of children with elevated dentine lead levels (> 20 ppm) fell below those expected based on their mothers' IQs and the amount by which a child's IQ fell below the expected value increased with increasing dentine lead levels in a nonlinear fashion. Scatter plots of IQ residuals by dentine lead levels and regression analyses for the control children with dentine below 10 ppm and for high-lead children with 20 to 29.9 ppm dentine lead did not reveal significant associations between increasing Pb levels in that range and IQ residuals, in contrast to statistically significant correlations between IQ residuals and dentine lead for high-lead group children with 30 to 39.9 ppm dentine lead levels.

Reanalyses of Needleman *et al.* (1979) study data have been done to correct certain methodological problems with some earlier published analyses. Needleman (1984), Needleman *et al.* (1985), and US EPA's Office of Policy and Analysis (1984) reported that the reanalyses confirm the published findings on significant associations between elevated dentine lead levels and decrements in IQ, after correcting data calculation errors detected in earlier published analysis and using alternative model specifications incorporating

better control for potentially confounding factors. The average magnitude of the full-scale IQ decrement attributable to lead was estimated in the 1979 analyses to be ~4 points after control for confounding factors. Based on the later reanalyses, the size of the full-scale lead effect remained about the same (i.e., around 4 points) after controlling for confounding variables. It is, however, very difficult to define quantitative dose–response relationships based on these data, beyond the statement that an average IQ decrement of about 4 points appears to be associated with lead exposure levels experienced by the high-lead group. Among that group, statistically significant IQ decrements appear to remain (after controlling for confounding variables) for children with 30 to 39.9 ppm dentine lead levels, but not for children with 20 to 29.9 ppm or lower dentine lead levels, as reported by Bellinger and Needleman (1983). Only limited data exist by which to estimate lead values likely associated with the observed IQ effects; that information points broadly toward an average PbB concentration in the 30 to 50 μg/dl range.

Bellinger *et al.* (1984b) later studied the academic performance of some children initially evaluated by Needleman *et al.* (1979). Of the 118 first and second grade children originally classified into low (< 10 ppm) and elevated (≧ 20 ppm) dentine lead groups, 70 were evaluated 4 years later. Also, 71 children with midrange dentine lead levels (10.0 to 19.9 ppm) were included in the follow-up investigation. Contemporary PbB levels could not be obtained. Four types of outcome measures were assessed: (1) standardized IQ measures, e.g., most recently available scores for the Otis–Lennon Mental Ability Test, as routinely administered by the school system; (2) teacher ratings, comprising a 24-item pupil-rating scale and the same 11-item scale used by Needleman *et al.* (1979); (3) indices of school failure, i.e., remedial instruction or grade retention; and (4) direct observation of classroom behaviour patterns reflecting inattention, distractibility, etc. Various statistical analyses suggested that grade retention was clearly associated with past dentine lead levels; and other outcomes showed the predicted direction of effect, but mostly at p values between 0.05 and 0.15. The teacher rating scale revealed no lead effect, a finding in contrast to earlier results of Needleman *et al.* (1979) and a more recent replication by Yule *et al.* (1984).

A study of urban children in Sydney, Australia (McBride *et al.*, 1982) involved 454 preschoolers (aged 4 to 5 y) with PbB levels of 2 to 29 μg/dl. PbB levels were evaluated at the time of neurobehavioural testing, but earlier exposure history was apparently not assessed. Using a multiple statistical comparison and Bonferroni correction to protect against study-wise error, no statistically significant differences were found between two groups with PbB levels more than one standard deviation above or below the mean (> 20 μg/dl versus < 9 μg/dl) on the Peabody Picture Vocabulary IQ Test, on Rutter's parent rating scale of hyperactivity, or on three tests of motor ability (pegboard, standing balance, and finger tapping). In one test of fine motor coordination (tracking), five-year-old boys in the higher lead group performed worse than boys in the lower lead group. In a test of gross motor skill (walking balance), results for the two age groups were conflicting. This study suffers from many methodological weaknesses and cannot be taken as providing evidence for or against an effect of low-level lead exposures

in non-overtly lead intoxicated children. For example, a comparison of socioeconomic status (father's occupation and mother's education) of the study sample with the general population showed that it was higher than Bureau of Census statistics for the Australian work force as a whole. Also, there was apparently some self-selection bias due to a high proportion of professionals living near the hospital where the children were born, and certain other important demographic variables (e.g., mother's IQ) were not evaluated.

Another large-scale study (Smith *et al.*, 1983) of tooth lead, behaviour, intelligence, and cognitive skills evaluated a general population sample of over 4000 children aged 6 to 7 years in three London boroughs. Of the 2663 children who donated shed teeth for analysis, 403 children were selected to form six groups, one each of high (8 μg/g or more), intermediate (5 to 5.5 μg/g), and low (2.5 μg/g or less) tooth lead levels for two socioeconomic groups (manual versus non-manual workers). Parents were intensively interviewed at home regarding parental interest and attitudes toward education and family characteristics and relationships. The early history of the child was then studied in school using tests of intelligence (WISC-R), educational attainment, attention, and other cognitive tasks. Teachers and parents completed the Conners behaviour questionnaires. Results showed that intelligence and other psychological measures were strongly related to social factors, especially social grouping. Lead level was linked to a variety of factors in the home, especially the level of cleanliness and, to a lesser extent, maternal smoking. Before correcting for confounding factors, there were significant associations between lead and full-scale IQ scores; however, upon correcting for confounding factors, there were no statistically significant associations between lead level and IQ or academic performance. Also, when rated by teachers (but not by parents), there were small, reasonably consistent (but not statistically significant) tendencies for high-lead children to show more behavioural problems after the different social covariables were taken into account statistically.

The Smith *et al.* (1983) study has much to recommend it: (1) a well-drawn sample of adequate size; (2) three tooth lead groupings based on well-defined classifications minimizing overlaps of exposure groupings based on whole-tooth lead values, including quality-controlled replicate analyses for the same tooth and duplicate analyses across multiple teeth from the same child; (3) PbB levels on a subset of 92 children which correlated reasonably well with tooth lead levels ($r = 0.45$); (4) cross-stratified design of social groups; (5) extensive information on social covariates and exposure sources; and (6) statistical control for potentially confounding covariates in the analyses of study results. It should also be noted that further statistical analyses of the Smith data, using tooth lead as a continuous variable or finer-grain categorization of subjects into eight tooth lead exposure groups, have recently been reported (Pocock and Ashby, 1985) to confirm no statistically significant associations between tooth lead and IQ across the entire spectrum of lead exposure levels present among the study population. Interestingly, the average full-scale IQ values for the medium- and high-lead groups in the Smith study were 2 points below the average value for the control group. Also, PbB values for

subsets of the children in the medium and high groups averaged 12 to 15 μg/dl (with all but one < 30 μg/dl) upon sampling within a few months of neuropsychological testing around age six. Somewhat higher PbB values might have been obtained if sampled at earlier ages for these children (given typical peaking of blood leads seen in preschool children), but they probably would have still fallen mainly in the 15 to 30 μg/dl range.

Harvey *et al.* (1983, 1984) reported a study involving 189 children, average age 2.5 years and 15.5 μg/dl PbB, from the inner city of Birmingham, England. A wide range of psychometric tests, behavioural measures of activity level, and psychomotor performance were used. Blood lead made no significant contribution to IQ decrements after appropriate allowance had been made for social factors, although, consistent with findings from the Lansdown *et al.* (1986) study discussed below, a stronger correlation between IQ and PbB levels was found in children of manual workers ($r = -0.32$) than in children of non-manual workers ($r = +0.06$). Strengths of this study are the following: (1) a well-drawn sample; (2) extensive evaluation of 15 confounding social factors; (3) a wide range of abilities evaluated; and (4) blind evaluations. The finding of no significant associations between lead and IQ decrements at the relatively low PbB levels evaluated are consistent with the results of Smith *et al.* (1983), discussed above, for children in the same exposure range.

Yule *et al.* (1981) conducted a pilot study of effects of low-level lead exposure on 85% of a cohort of 195 children aged 6 to 12 years, whose PbB concentrations were determined nine months earlier as part of a European Economic Community survey. The PbB concentrations ranged from 7 to 32 μg/dl; 11 to 12 μg/dl; 13 to 16 μg/dl; and 17 to 32 μg/dl. The tests of achievement and intelligence were similar to those used in studies by Lansdown *et al.* (1974) and Needleman *et al.* (1979). Significant associations were found between PbB levels and decrements in IQ (full-scale IQ scores averaged ~ 7 points lower for the highest lead group), as well as lower scores on tests of reading and spelling, but not mathematics (Yule *et al.*, 1981). These differences in performance (although reduced in magnitude) largely remained statistically significant at $p < 0.05$ after age, sex, and father's occupation were taken into account. However, other potentially confounding social factors such as parental IQ were not controlled in this study, and the investigators cautioned against interpretation of their results as evidence of relationships between lead and IQ or functioning at school without further confirmatory results after better control for social factors.

Lansdown *et al.* (1986) replicated their earlier pilot study (Yule *et al.*, 1981) with 194 children ($\bar{X}$ age = 8.8 y) living in a mainly working-class area of London near a busy roadway. In this second, better designed study, a lengthy structured interview yielded data on sources of exposure, medical history, and many potentially confounding variables, including parental IQ and social factors. Analyses of covariance were used to evaluate the effects of lead and other factors on WISC-R verbal, performance, and full-scale IQ scores, as well as reading accuracy and comprehension scores, for children with low (7 to 12 μg/dl) versus elevated (13 to 24 μg/dl) PbB levels. No significant lead effect was evident even before considering social class. However, there was some suggestion of a trend in effects on IQ in the children of manual workers

when compared with children of non-manual workers.

In another study, Yule and Lansdown (1983) evaluated 302 children ($\bar{X}$ age = 9 y) living in Leeds, England. Tests and procedures similar to those employed in the previous two studies were used and, in addition, a reaction time test was employed (Hunter *et al.*, 1985). The Leeds children were divided, for statistical analyses of the data, by (1) social class (manual versus non-manual) and (2) blood lead level (low = 5 to 11 μg/dl; high = 12 to 26 μg/dl). As in the London replication study, no statistically significant relationships for any of the IQ or reading performance scores were found even before social class was controlled for in the statistical analyses. The high-lead children averaged nearly identical or slightly better than control subjects on several outcomes. However, small but statistically significant ($p < 0.05$) changes in reaction time (shorter for 3-s delays; longer for 12-s delays) were found and paralleled similar reaction time effects of larger magnitude found by Needleman *et al.* (1979) for American children with higher lead exposures. Analysis of covariance, controlling for age, revealed that the reaction-time differences between low- and high-lead children in Leeds were only significant for the younger children (aged 6 to 10 y) but not for the older children (aged 11 to 14 y). Yule *et al.* (this volume) have extended these findings and developed other assessments of neurobehavioural function in lead-exposed children with some interesting preliminary resutls.

Yule *et al.* (1984) also used three different teacher questionnaires (Needleman, Rutter, and Conners) to assess attention deficits in the same children evaluated in their earlier report (Yule *et al.*, 1981). While there were few differences between groups on the Rutter scale, the summed scores on the Needleman questionnaire across the PbB groupings approached significance ($p = 0.096$). Three of the questionnaire items showed a significant dose–response function ("Day Dreamer", "Does not Follow Sequence of Direction", "Low Overall Functioning"). Nine of 11 items were highly correlated with children's IQ. Therefore, the Needleman questionnaire may be tapping IQ-related attention deficits as opposed to measures of conduct disorder and socially maladaptive behaviour (Yule *et al.*, 1984). The hyperactivity factors of the Conners and Rutter scales were reported to be related to PbB levels (7 to 12 versus 13 to 32 μg/dl), but the authors noted that caution is necessary in interpreting their findings in view of the crude measures of social factors available and the differences between countries in diagnosing attention deficit disorders. Also, since the PbB values reported were determined only once (nine months before psychological testing), earlier lead exposure may not have been fully reflected in the reported PbB levels; however, even if higher earlier, the PbB values would likely have still fallen mainly in the 15 to 30 μg/dl range for the higher two quartile groups.

Two reports by Schroeder and colleagues (Schroeder *et al.*, 1985; Schroeder and Hawk, 1987) are of particular importance for the issue of lead's effects on children's cognitive functioning. Although these studies dealt with children identified through lead-screening programmes or who were potentially at risk for elevated lead exposure, actual PbB levels in these children were close to or not much higher than levels in the above general population studies. Schroeder *et al.* (1985) evaluated 104 lower SES children in North Carolina,

ages 10 months to 6.5 years. About half of the children (aged < 30 months) were tested on the Bayley Scales of Mental Development; the rest of the subjects (age > 30 months) were tested on the Stanford–Binet Intelligence Scale. Several other variables were also assessed, including Caldwell and Bradley (1979) HOME scores and parental IQ, SES, education, and employment. Venous blood samples obtained on the day of testing ranged from 6 to 59 μg/dl ($\bar{X} \approx 30$ μg/dl). Statistical analysis of the data involved a form of hierarchical backward stepwise regression. Lead was found to be a significant ($p < 0.01$) source of effect on IQ scores in these children after controlling for SES, HOME score, maternal IQ, and other social factors. SES was the only other variable to reach statistical significance ($p < 0.001$); other variables apparently failed to reach significance because of collinearity with SES. A corollary study of the same children by Milar *et al.* (1981) found no association between lead exposure and hyperactivity. Fifty of the children were re-examined 5 years later, at which time all PbB levels were < 30 μg/dl. In addition to re-evaluating the children with the Stanford–Binet IQ test, the investigators repeated SES and maternal IQ (but not HOME) measurements. Although the 5-year follow-up IQ scores were negatively correlated with both contemporary and initial PbB levels, the lead effect was not significant after covariates (especially SES) were included in the regression model. It is interesting to note also that the correlation between maternal and child IQ was only ~0.06 for children with initial PbB levels of 31 to 56 μg/dl, but returned to a nearly normal value of 0.45 after 5 years, when PbB levels had dropped. Similar findings were reported by Perino and Emhart (1974) and Bellinger and Needleman (1983), and have been used to argue that an environmental factor (i.e., lead) disrupts the normal mother–child IQ correlation of ~0.50. Thus, this Schroeder *et al.* (1985) finding provides further, indirect evidence of lead's disruptive effect on children's cognitive functioning at PbB levels in the range of ~30 to 60 μg/dl.

Schroeder and Hawk (1987) replicated the above study with 75 black children from North Carolina, all of low SES and aged 3 to 7 years. Blood lead levels averaged 21 μg/dl (range: 6 to 47 μg/dl). Backward stepwise multivariate regression analysis revealed a highly significant relationship between contemporary PbB level and IQ ($p < 0.0008$); the effect was nearly as striking ($p < 0.002$) whether maximum or mean PbB values (from health department records) were used. No other covariate achieved significance at $p = 0.05$ in this analysis, although maternal IQ was closest. SES was not a significant covariate in this study because SES was uniformly low. (Further analyses showed HOME scores to be significantly correlated with PbB levels and to be collinear with maternal IQ and SES.) The effect of PbB level on IQ appeared to extend linearly across the entire range of PbB concentrations. In fact, 78% of the subjects had PbB levels below 30 μg/dl. More details on the Schroeder studies are provided elsewhere in these proceedings.

In another study discussed elsewhere in this volume, Fulton *et al.* (1987) evaluated cognitive abilities and educational attainment in a population of school-age children from central Edinburgh, Scotland. The geometric mean average PbB level for the 501 children in the study sample was 11.5 μg/dl (range 3.3–34.0 μg/dl). Multiple regression analyses indicated significant

relationships between log-transformed PbB levels and composite scores on the British Ability Scales and between PbB levels and attainment test scores for quantitative and reading skills, with allowance for 33 possible confounding variables. Grouping the subjects by PbB levels showed a clear dose–response relationship without any evident threshold down to the lowest subgroup mean PbB level of 5.6 μg/dl.

Silva *et al.* (1988) investigated cognitive development and behaviour problems in 579 11-year-old children in Dunedin, New Zealand. Higher SES groups were significantly over-represented in this sample, but the correlation between PbB levels and SES was near zero. The mean PbB level at age 11 was 11.1 μg/dl (SD = 4.91). No significant effects on IQ were evident from an analysis of WISC-R scores. Regression analyses and multiple correlations were performed on scores from a reading ability test, the Rutter parent and teacher questionnaires, and other assessments of children's inattention and hyperactivity derived from parent and teacher reports. The contribution of PbB levels to the explained variance for the reading ability scores was non-significant. However, five of the six remaining assessments of children's behaviour showed significant increases in the amount of explained variance when the PbB variable was added. Although PbB accounted for only 0.8 to 1.2% of the additional variance, the results nonetheless indicate some association between lead exposure and small but significant adverse effects on behaviour in older children, even after allowance for certain background factors (e.g., maternal verbal ability, maternal depression, a composite index of social disadvantage). Another report by Silva *et al.* (1986) noted that some of the children in the Dunedin pilot study had had significant exposure to lead through paint-stripping activities in the home. Although only two subjects had PbB levels above 30 μg/dl at the time of testing, this information highlights the need for earlier and more precise histories of long-term lead exposure for accurate interpretation of the Dunedin findings.

The general population studies reviewed here do not individually provide definitive evidence for or against neuropsychological deficits being associated with low body lead burdens in non-overtly lead-intoxicated children representative of general paediatric populations. However, the overall pattern of results certainly substantiates such an association, with two recent studies (Schroeder and Hawk, 1987; Fulton *et al.*, 1987) especially indicating a highly significant linear relationship between measures of IQ and PbB levels over a broad range (6–47 μg/dl and 3–34 μg/dl, respectively). In the Schroeder and Hawk study this effect was almost equally as strong regardless of whether contemporary, past maximum, or mean PbB levels were used in the analysis. Because the subjects were all black children of uniformly low socioeconomic status, SES was not a significant covariate in the analysis. It is possible that SES and lead exposure interact such that IQ is affected by PbB at lower SES levels but not at higher SES levels (*cf.* Schroeder *et al.*, 1985). Findings of stronger correlations between IQ and PbB levels in children of manual working class fathers (Harvey *et al.*, 1983, 1984; Yule and Lansdown, 1983; Lansdown *et al.*, 1986) are consistent with this hypothesis (*cf.* Winneke and Kraemer, 1984). If true, this interactive relationship would suggest that lower SES places children at greater risk for deleterious effects of low-level lead

exposure on cognitive ability. However, as results from Schroeder *et al.* (1985) and Schroeder and Hawk (1987) indicate, other variables such as HOME scores and maternal IQ may covary with SES. Other work (e.g., Milar *et al.*, 1980; Dietrich *et al.*, 1985) points to the home environment as a significant predictor of lead exposure. This close relationship between SES, quality of home environment, and lead exposure suggests that low SES may not be the sole determiner of increased risk for cognitive impairment. (See also the discussion by Bellinger *et al.*, 1986b, and elsewhere in this volume.) Further research is needed to disentangle the relative contributions of these variables to the neurotoxic effects of lead.

In regard to the magnitude of lead effects on IQ, the Needleman analyses point toward full-scale IQ deficits of about 4 points and other neurobehavioural deficits in American children being associated with lead exposures resulting in dentine lead values above 20 to 30 ppm and likely average PbB values in the 30 to 50 μg/dl range. The report of recent analyses by Schroeder *et al.* (1985) further supports this conclusion, even after the major influence of SES was allowed for in the analyses. However, their findings indicate that the effect of PbB on IQ could not be detected five years after the original assessment. A follow-up by Bellinger *et al.* (1984b) of the children studied by Needleman *et al.* (1979) suggests that other measures of classroom performance may show long-term effects of early lead exposure more effectively than IQ measures (see also Silva *et al.*, 1988). Shaheen (1984) has also questioned the sensitivity of IQ scores and has suggested that the variability of outcomes of studies of lead's effects on neuropsychological functioning in children may relate to differences in the ages at which children are subjected to toxic lead exposures.

For the most part, the remaining general population studies reviewed in this section report a lack of statistically significant effects on IQ or other neuropsychological measures. Most of those studies found slightly lower IQ scores for higher-lead exposure groups than for low-lead control groups before correcting for confounding variables, but the differences were typically reduced to 1 to 2 IQ points and were non-significant (usually even at $p < 0.10$) upon correction for confounding factors. The following conclusions may be stated about these latter results: (1) they tend to suggest relatively minimal effects of lead on IQ in general populations, especially in comparison to much larger effects of other factors (e.g., social variables), at the exposure levels evaluated in the studies (PbB values mainly in the 15 to 30 μg/dl range); and (2) they are not incompatible with other findings of significant lead effects on IQ at higher average PbB levels (≥ 30 μg/dl).

Exceptions to the general pattern noted above are beginning to emerge and warrant comment here. Specifically, Schroeder and Hawk's findings for a population of low-SES US children complement those of Fulton *et al.* for a relatively more affluent population in Edinburgh. The average and range of PbB levels in the Edinburgh study were somewhat lower than those in the Schroeder and Hawk study: 11.5 μg/dl (3.3–34.0 μg/dl) in Edinburgh versus 21 μg/dl (6–47 μg/dl) in North Carolina. Even so, Fulton *et al.* reported significant lead-related effects on covariate-adjusted scores of cognitive ability and educational attainment. Since only 2% of the Edinburgh study sample

had PbB levels above 25 μg/dl and since a dose–response analysis showed no evident threshold (down to an average PbB level of 5.6 μg/dl) for either ability or attainment scores, these findings, in conjunction with the results of Schroeder and Hawk, point to notable deficits in cognitive performance at PbB levels well below 30 μg/dl and possibly extending to levels below 10 μg/dl. However, as with other cross-sectional studies, a complete history of past blood lead levels was not obtained, and so the possibility remains that a higher degree of lead exposure at some earlier period of development (and not reflected by contemporary PbB levels) was responsible for the outcomes measured in these studies. Also, the findings of altered reaction time patterns by Hunter *et al.* (1985), which parallel those reported by Needleman at higher exposure levels, are notable and appear to argue for probable effects of lead on attention or vigilance functions at levels extending below 30 μg/dl and, possibly, down to as low as 15 to 20 μg/dl.

Other recent cross-sectional studies of neurobehavioural performance in general populations of children are described elsewhere in this volume by Cludyts, Hansen *et al.*, and Vivoli *et al.* These studies also point to deficits in neurobehavioural function at relatively low levels of lead exposure, primarily reflected by tooth lead concentration as an indicator of cumulative lead exposure.

Smelter area studies

Smelter studies evaluated children with elevated lead exposures associated with residence in cities or elsewhere in close proximity to lead-emitting smelters. Most of the early studies, conducted in the 1970s, found mixed results even though evaluating children with PbB levels typically in excess of 30 μg/dl. Because of methodological weaknesses, however, most of the early studies must be viewed as inconclusive. For example, in an early study of this type, Lansdown *et al.* (1974) reported a relationship between PbB level in children and the distance they lived from lead-processing facilities, but no relationship between PbB level and mental functioning. However, only a minority of the lead-exposed cohort had PbB levels markedly differing from control subjects with elevated PbB levels (< 40 μg/dl), and the study did not adequately control for important confounding factors.

In another study, Landrigan *et al.* (1975) found the lead-exposed children living near an El Paso, Texas, smelter scored significantly lower than matched controls on measures of performance IQ and finger–wrist tapping. The control children in this study were, however, not well matched by age or sex to the lead-exposed group, although the results remained statistically significant after adjustments were made for age differences. In contrast, NcNeil and Ptasnik (1975) found little evidence of lead-associated decrements in cognitive abilities in another sample of children living near the same El Paso smelter. These children were generally comparable medically and psychologically to matched controls living elsewhere in the same city, but for direct effects of lead (PbB level, free erythrocyte protoporphyrin levels, and X-ray findings). An extensive critique of these two El Paso studies was performed by an

expert committee (see Muir, 1975), which concluded that no reliable conclusions could be drawn from either of the published studies in view of various methodological and other problems affecting their conduct and statistical analyses.

A study by Ratcliffe (1977) of children living near a battery factory in Manchester, England found no significant associations between PbB levels sampled at two years of age (28 μg/dl versus 44 μg/dl in low- versus high-lead groups) and testing done at age five on the Griffiths Mental Development Scales, the Frostig Developmental Test of Visual Perception, a pegboard test, or a behavioural questionnaire. The scores, although not very different in magnitude, were somewhat better for the low-lead exposure children than for the higher exposure group. The small sample size (23 low-lead and 24 high-lead children), inadequate control for parental IQ, and the failure to repeat PbB assays at age five weaken this study. Variations in PbB levels occurring after age two among control children may have lessened exposure differences between the low- and high-lead groups, and larger sample sizes would have better allowed for detection of any lead effects present.

More recent smelter studies provide assessments that accord greater attention to control for potentially confounding factors, and many also assessed larger samples of children, allowing for more power to detect lead effects. Two studies by Winneke and colleagues, the first a pilot study (Winneke *et al.*, 1982) and the second an extended study (Winneke *et al.*, 1983), used tooth lead analyses analogous to some studies described above. In the pilot study, incisor teeth were donated by 458 children aged 7 to 10 years in Duisburg, Germany, an industrial city with airborne lead concentrations of 1.5 to 2.0 μg/m^3. Two extreme exposure groups were formed, a low-lead group with 2.4 μg/g mean tooth lead level ($n = 26$) and a high-lead group with 7 μg/g mean tooth lead level ($n = 16$). These groups were matched for age, sex, and father's occupational status. The two groups did not differ significantly on confounding covariates, except that the high-lead group showed more perinatal risk factors. Parental IQ and quality of the home environment were not among the 52 covariables examined. The authors found a marginally significant decrease ($p < 0.10$) of 5 to 7 IQ points and a significant decrease in perceptual–motor integration ($p < 0.05$), but no significant differences in hyperactivity as measured by the Conners Teachers' Questionnaire. As with the Yule *et al.* (1981) study, the inadequacy of statistical or other control for background social variables and parental IQ (as well as group differences in perinatal factors) weaken this study; the investigators cautioned against interpretation of their results as evidence for low-level lead effects in the absence of further, confirmatory results from larger, better controlled studies.

In their second study, Winneke *et al.* (1983) evaluated 115 children ($\bar{X}$ age: 9.4 y) living in the lead smelter town of Stolberg, Germany. Tooth lead ($\bar{X}$: 6.16 ppm, range: 2.0 to 38.5 ppm) and PbB levels ($\bar{X}$: 13.4 μg/dl; range: 6.8 to 33.8 μg/dl) were significantly correlated ($r = 0.47$; $p < 0.001$) for the children studied. Using stepwise multiple regression analysis, the authors found significant ($p < 0.05$) or marginally significant ($p < 0.10$) associations between tooth lead and measures of perceptual–motor integration, reaction-

time performance, and four behavioural rating dimensions, including distractibility, even after controlling for age, sex, duration of labour at birth, and socio-hereditary background. However, the proportion of explained variance due to lead never exceeded 6% for any of these outcomes, and no significant association was found between tooth lead and WISC verbal IQ after the effects of socio-hereditary background were eliminated.

A third study by Winneke *et al.* (1984) evaluated neuropsychological functioning and neurophysiological parameters for 122 children (aged 6 to 7 y) living in the Nordenham, FRG area. Performance on various neuropsychological tests (shortened form of the Hamburg–Wechsler IQ test; reaction-behaviour and reaction-time tests, etc.) was evaluated in relation to both concurrently sampled PbB values ($\bar{X} = 8\ \mu g/dl$; max. $= 23\ \mu g/dl$) and umbilical cord PbB levels (max. $= 31\ \mu g/dl$). A variety of potentially confounding factors (such as socio-hereditary variables, pre- and postnatal risk factors, etc.) were also assessed and taken into account in a series of stepwise multiple regression analyses in which the effects of confounding factors were successively eliminated and the lead effects then checked for significance. No significant associations (at $p < 0.05$) were found between either umbilical cord or current PbB levels and verbal, performance, or total IQ scores estimated from the Hamburg–Wechsler subtests (only the correlation for performance IQ with current PbB level reached $p < 0.10$). On the other hand, much larger and highly significant correlations were found between socio-hereditary factors and all three types of IQ scores. The investigators remarked on the heavy dependence of the IQ measurements on the social environment and noted that, as in their prior large-scale study (Winneke *et al.*, 1983), it was not possible to convincingly show a lead-dependent decrease in intelligence. Nor were any lead effects found on the Goettinger shape reproduction test of psychomotor performance or for various reaction-time measures. Only in the case of reaction behaviour, as indexed by increased errors on the Wiener (Vienna) serial stimulus reaction test, were significant deficits in neuropsychological functioning detected at the low exposure levels (PbB < 25 to $30\ \mu g/dl$) evaluated in this study. Certain statistically significant effects on electrophysiological measures of neurophysiological functioning were also observed. Retesting of 76 of the Nordenham children at age 9, with PbB levels approximately equal to those measured 3 years earlier, indicated persisting lead-related deficits in performance on the Wiener reaction test (see Winneke *et al.*, this volume).

Hatzakis *et al.* (this volume) also conducted neuropsychological testing on more than 500 children living near a lead smelter in Lavrion, Greece, and found impairments in WISC-R IQ scores and reaction performance scores, including performance on the Wiener reaction device. These effects were significantly associated with PbB levels after controlling for 17 covariates, including parental IQ, in a multiple regression model. Blood lead concentrations ranged from 7.4 to $63.9\ \mu g/dl$ and averaged 23.7. Grouping of subjects by PbB levels showed dose–response relationships for IQ as well as reaction performance scores, with no evident threshold for reaction performance effects.

The above smelter area studies, particularly the more recent, better

conducted studies of populations with average PbB levels well below $30\ \mu g/dl$, supplement findings from general population studies of neurobehavioural function in children. Although the Hatzakis study provides additional evidence of IQ deficits in children with PbB levels $< 30\ \mu g/dl$, the strongest effects to emerge from these studies appear to be in the area of reaction performance. As such, these findings are consistent with the results of Hunter *et al.* (1985) and Needleman *et al.* (1979) and point to lead-induced neurobehavioural effects in children at PbB levels below $30\ \mu g/dl$, possibly extending to as low as $15\ \mu g/dl$.

Studies of neuropsychiatrically disordered children

Rather than starting with a known lead-exposed population and attempting to discover evidence of neurobehavioural dysfunction, a number of studies have first identified a population with some recognized disorder and then looked for evidence of elevated lead exposure. For example, a series of studies by David *et al.* (1974; 1976a,b; 1977; 1979a,b; 1982a,b; 1983; 1985) measured lead levels in diagnosed hyperkinetic children and showed an association between hyperactivity and elevated lead levels. However, whether a disorder such as hyperactivity is the effect or the cause of elevated lead exposure is difficult to resolve. It is possible, for example, that hyperactive children might ingest more lead than normal children because of a greater incidence of pica or because they stir up more dust-borne lead by their activity. David *et al.* (1977) reported that PbB levels of hyperactive children with a probable aetiology of an organic nature were lower than those of children with no apparent cause (other than lead). This finding suggests that hyperactivity does not necessarily result in elevated lead exposure, but it does not rule out the possibility of a third factor causing both hyperactivity and elevated PbB levels (see discussion of Gittelman and Eskenazi, 1983, below). Also, a problem common to the studies in question is the lack of adequate information on the children's past lead exposure, particularly during preschool years when children tend to be at greatest risk for higher exposure levels. As David *et al.* (1976a) have acknowledged, it is difficult to establish an aetiological relationship between lead and behavioural disorders on the basis of retrospective estimations of lead exposure.

Another study by David *et al.* (1983) appeared to obviate some correlational approach problems by experimentally manipulating body lead levels, i.e., by reducing PbB concentrations through the administration of a chelating agent, penicillamine. The objective was to determine if decreases in body lead burden would be accompanied by improvements in children's hyperactive behaviour, and in short, this was essentially the conclusion drawn by David and his colleagues. In addition, the study compared the effect of the chelating agent with a therapeutic drug of known efficacy, methylphenidate, and found the two treatments to be roughly equivalent in reducing symptoms of hyperactivity. Although this study was in many respects well designed and executed, certain problems nevertheless cloud its interpretation. As noted by Needleman and Bellinger (1984), the number of subjects per treatment group was rather

limited (maximum of 31) and quite unbalanced due in part to a high and disproportionate subject attrition rate. Subjects were particularly prone to drop out of the placebo group, and this imbalance was exacerbated by a 'chance preponderance' of subjects assigned to the penicillamine treatment and by later reassignment of some placebo and methylphenidate subjects to the penicillamine group. Questions also arise concerning the appropriateness of the statistical treatment of data by David *et al.* (1983). For example, multivariate analysis of variance (MANOVA) would seem to be more appropriate than separate ANOVAs and multiple *t*-tests applied to the various outcome measures used to assess the children's behaviour. Use of MANOVA would also have helped alleviate the problem of regression toward the mean, which in this case may have created the false impression that 'improvements' in behaviour, i.e., changes toward more normal behaviour, were due to an effect of the treatment. Rutter (1983, p. 313) has also noted that David's multiple group comparisons are not as convincing as an analysis that would utilize individual PbB values and behaviour scores (presumably, multivariate regression analysis). Finally, as David *et al.* (1983) themselves point out, it is clear that lead could be only one of several aetiological factors in the causation of hyperkinesis or attention deficit disorders in children and that, at best, their findings pertain only to recognized hyperactive children, not to the general population.

An attempt by Gittelman and Eskenazi (1983) to replicate earlier work by David *et al.* (1974, 1977) was only partly supportive of the latter's findings. A large group of hyperactive children ($n = 103$) showed a trend ($p = 0.06$) toward higher chelated lead levels in their urine, but a clear-cut ($p = 0.02$) elevation in lead levels was evident only in paired comparisons with 33 non-hyperkinetic siblings. As Gittelman and Eskenazi (1983) noted, this finding raises the question of why the hyperactive children had higher lead levels than their siblings, given that they shared the same water, air, and home environment. The possibility of a third factor, e.g., a metabolic difference that might affect the ability to excrete lead as well as the occurrence of hyperactivity, cannot be dismissed.

A study of 98 Swedish children with various minor neuropsychiatric disorders (e.g., perceptual–motor dysfunctions, speech disorders, attention-deficit problems) found no correlation between the children's disorders and their tooth lead levels (Gillberg *et al.*, 1982). However, comparing the 10 highest and 10 lowest lead-burdened children did reveal a significant difference in a clinical measure of their mean reaction times.

Youroukos *et al.* (1978) compared PbB as well as ALA-D values of 60 Greek children with mental retardation of unknown aetiology against 30 mentally retarded children with a known aetiology and 30 normal children. The average values of the mentally retarded children with unknown aetiology were significantly different from both the other groups in two regards: their mean PbB level was higher (30 μg/dl versus 21 μg/dl in both control groups) and, in 24 patients with elevated (≥ 40 μg/dl) PbB levels, ALA-D activity was significantly lower. Although pica was noted to be common in both groups of mentally retarded children, no child in the study was known to have ever been lead-poisoned.

Work in Scotland has provided information tending to link prenatal lead exposures to the later development of mental retardation. Beattie *et al.* (1975) identified 77 retarded children and 77 normal children matched on age, sex, and geography. The residence during the gestation of the subject was determined, and a first-flush morning sample of tap water was obtained from the residence. Of 64 matched pairs, no normal children were found to come from homes served with water containing high lead levels (> 800 μg/L), whereas 11 of the 64 retarded children came from homes served with such high-lead water. The authors concluded that pregnancy in a home with high lead in the water supply increases by a factor of 1.7 the risk of bearing a retarded child. In follow-up work, Moore *et al.* (1977) obtained lead values from blood samples drawn during the second week of life from children studied by Beattie *et al.* The samples were obtained as part of routine screening for phenylketonuria and kept stored on filter paper. Blood samples were available for 41 of the retarded and 36 of the normal children in the original study by Beattie *et al.* (1975). PbB concentrations in the retarded children were significantly higher than values measured in normal children: the mean for retardates was 1.23 ± 0.43 μmol/L (25.5 ± 8.9 μg/dl) and for normals was 1.0 ± 0.38 μmol/L (20.9 ± 7.9 μg/dl). The difference in PbB levels was significant ($p = 0.02$) by the Mann–Whitney test.

These latter two studies suggest that fetal lead exposure during the critical period of brain development may cause perturbations in brain organization that are expressed later in mental retardation syndromes, and they raise for careful scrutiny the issue of postnatal risks associated with intrauterine exposure to lead. Long-term prospective studies of the type described later are beginning to produce results which address that issue.

Studies of association of neuropsychological effects and hair lead levels

Several studies have reported significant associations between hair lead levels and behavioural or cognitive testing endpoints (Pihl and Parkes, 1977; Hole *et al.*, 1979; Hansen *et al.*, 1980; Capel *et al.*, 1981; Ely *et al.*, 1981; Thatcher *et al.*, 1982; Marlowe *et al.*, 1982, 1983, 1985; Marlowe and Errera, 1982). Measures of hair lead are easily contaminated by external exposure and are generally questionable in terms of accurately reflecting internal body burdens (see Chapter 9 of US EPA, 1986a). Such data, therefore, cannot be credibly used to evaluate relationships between absorbed lead and nervous system effects, and they are not discussed further here.

ELECTROPHYSIOLOGICAL STUDIES OF LEAD EFFECTS IN CHILDREN

In addition to psychometric and behavioural approaches, electrophysiological studies of lead neurotoxicity in non-overtly lead-intoxicated children have been conducted. One such study (Thatcher *et al.*, 1984) reported significant

effects on various measures of auditory and visual evoked potentials in lead-exposed children, but the only measure of lead exposure was hair lead, which, as previously noted, is not a suitable index of lead exposure.

Burchfiel *et al.* (1980) used computer-assisted spectral analysis of a standard EEG examination on 41 children from the Needleman *et al.* (1979) study and reported significant EEG spectrum differences in percentages of alpha and low-frequency delta activity in spontaneous EEGs of the high-lead children. Percentages of alpha and delta frequency EEG activity and results for several psychometric and behavioural testing variables (e.g., WISC-R full-scale IQ and verbal IQ, reaction time under varying delay, etc.) for the same children were then employed as input variables (or 'features') in direct and stepwise discriminant analyses. The separation determined by these analyses for combined psychological and EEG variables ($p < 0.005$) was reported to be strikingly better than the separation of low-lead from high-lead children using either psychological ($p < 0.041$) or EEG ($p < 0.079$) variables alone. Unfortunately, no dentine lead or PbB values were reported for the specific children from the Needleman *et al.* (1979) study who underwent the EEG evaluations reported by Burchfiel *et al.* (1980). Lead-exposure levels associated with the observed EEG effects would appear likely to fall within the same broad 30 to 50 μg/dl PbB range estimated earlier for the Needleman IQ deficit observations.

Guerit *et al.* (1981) examined 79 11-year-old children attending three different schools near a lead smelter and presenting PbB levels up to 44 μg/dl (averaging less than 30 μg/dl). Children from two distant urban and rural schools served as controls. A neurophysiological function score for each child was based on measures of EEGs, visual evoked potentials, brainstem auditory evoked potentials, and eye movements. Neurophysiological scores were negatively correlated ($p < 0.05$ by Spearman rank correlation coefficient) with PbB and FEP levels for the children from one of the smelter area schools, but the authors attributed this finding to the inclusion of four children who were left-handed or suffering from external ear pathology. Chi-square tests of neurophysiological scores as a function of PbB or FEP groupings based on the total study population were all non-significant. Note that comparatively low-power non-parametric statistical tests were employed in this study because of the qualitative or ordinal nature of the data. However, the use of more detailed quantitative measures of neurophysiological function would have enabled the investigators to employ more powerful parametric statistics, with possibly different outcomes from their analyses.

The relationship between low-level lead exposure and neurobehavioural function (including electrophysiological responses) in children aged 13 to 75 months was extensively explored in another study, conducted by the University of North Carolina and the US Environmental Protection Agency. Psychometric evaluation revealed a significant lead-related IQ decrement at the time of initial evaluation (Schroeder *et al.*, 1985), as noted previously. No relationship between PbB and hyperactive behaviour (as indexed by standardized playroom measures and parent–teacher rating scales) was observed in these children (Milar *et al.*, 1981). On the other hand, electrophysiological assessments, including analyses of low cortical potentials during

sensory conditioning (Otto *et al.*, 1981) and EEG spectra (Benignus *et al.*, 1981), did provide evidence of lead CNS effects in the same children. A significant linear relationship between PbB (ranging from 6 to 59 μg/dl) and slow wave voltage during conditioning trials was observed (Otto *et al.*, 1981). Analyses of quadratic and cubic trends, moreover, did not reveal any evidence of a threshold for this effect. The slope of the PbB × slow wave voltage function, however, varied systematically with age. No effect of PbB on EEG power spectra or coherence measures was observed, but the relative amplitude of synchronized EEG between left and right hemispheres (gain spectra) increased relative to PbB levels (Benignus *et al.*, 1981). A significant cubic trend for gain between the left and right parietal lobes was found with a major inflection point at 15 μg/dl. This finding suggests that EEG gain is altered at PbB levels as low as 15 μg/dl, although the clinical and functional significance of this measure has not been established.

A follow-up study of slow cortical potentials and EEG spectra in a subset (28 children aged 35 to 93 months) of the original sample was carried out two years later (Otto *et al.*, 1982). Slow wave voltage during sensory conditioning again varied as a linear function of blood lead, even though the mean lead level had declined by 11 μg/dl (from 32.5 μg/dl to 21.2 μg/dl). Although the EEG gain effect did not persist, the similarity of slow wave voltage results obtained at initial and follow-up assessments suggests that the observed alterations in this parameter of CNS function were persistent, despite a significant decrease in the mean PbB level during the two-year interval.

In a five-year follow-up study on a subset of the same children, Otto *et al.* (1985) found that slow wave voltage varied as a function of current PbB level during active conditioning, but not during the passive conditioning test used in earlier studies. In the passive test, a tone was paired with a short blackout of a silent cartoon. The active test was similar except that children pressed a button to terminate the blackout and resume the cartoon. Although the brain response elicited by the active test is greater than that produced by the passive test, the active test cannot be performed reliably by children under five years of age.

In addition to the experimental conditioning tests, Otto *et al.* (1985) used two clinically validated measures of sensory function, the pattern-reversal visual evoked potential (PREP) and the brainstem auditory evoked potential (BAEP). Exploratory analysis of PREPs revealed increased amplitude and decreased latency of certain components as a linear function of original PbB levels. Although these results were contrary to predictions, the findings are consistent with the results of Winneke *et al.* (1984), who found an association between increased PbB levels and decreased latency in the primary positive component of PREPs in children. BAEP results of the five-year follow-up study also indicated significant associations between original PbB levels and increased latencies of two components (waves III and V), indicative of auditory nerve conduction slowing.

Otto and his coworkers (Otto, 1985; Robinson *et al.*, 1985) also reported results of a replication study with an independent group of children 4 to 7 years old; PbB levels ranged from 6 to 47 μg/dl at the time of testing.

Psychometric data from this study (Schroeder and Hawk, 1987) have been reviewed above. Sensory conditioning was limited to the passive test due to the age range of the children. Contrary to earlier findings (Otto *et al.*, 1981, 1982), slow wave voltage did not vary with PbB levels. Differences between the two groups studied, however, may have contributed to the discordant results. Children in the earlier studies were somewhat younger (1 to 6 versus 3 to 7 years) and were exposed by different routes (secondary occupational exposure versus lead paint and contaminated soil) than children in the replication study (see review by Otto, 1985). More recent analyses of these slow wave data and their implications, as well as other results, are discussed by Otto elsewhere in this volume.

Results from Otto's replication study also indicated that hearing threshold, a reflection of peripheral auditory system function, increased directly with lead levels. Although hearing threshold did not vary with blood lead level in the five-year follow-up study (Otto *et al.*, 1985), this finding bears further investigation in view of other reports suggesting impaired auditory processing in lead-exposed children (de la Burde and Choate, 1975; Needleman *et al.*, 1979); and in fact, additional new analyses reported elsewhere in this volume by Otto and by Schwartz and Otto (1987) provide further evidence for lead-induced auditory system effects.

In summary, these electrophysiological studies provide emerging evidence for lead-related effects on CNS function in children at PbB levels considerably below 30 μg/dl, but inconsistent findings across studies require clarification. Linear dose–response relations have been observed in slow wave voltage during conditioning (Otto *et al.*, 1981, 1982, 1985), BAEP latency (Otto *et al.*, 1985), PREP latency (Otto *et al.*, 1985; Winneke *et al.*, 1984), and PREP amplitude and direction of effect varied across studies. Sensory evoked potentials, in particular, hold considerable promise as sensitive, clinically valid nervous system measures unaffected by social factors that tend to confound traditional psychometric measures (Halliday and McDonald, 1981; Prasher *et al.*, 1981). BAEPs, for instance, are not altered by changes in attention or level of consciousness. Reliable BAEPs can be recorded in (sedated) children between the ages of one and five, the most vulnerable period for lead poisoning as well as the most difficult period for most types of neurobehavioural testing. The current electrophysiological evidence concerning lead exposure and brain function in children, however, is too fragmentary to draw any firm conclusions. The use of evoked potential measures in prospective paediatric lead studies would provide a useful adjunct to other neurobehavioural tests and would help to better establish any neurobehavioural threshold for lead toxicity.

The adverse effects of lead on peripheral nerve function in children remain to be considered. Lead-induced peripheral neuropathies, although often seen in adults after prolonged exposures, are rarely noted in children. Several articles (Anku and Harris, 1974; Erenberg *et al.*, 1974; Seto and Freeman, 1964), however, describe case histories of children with lead-induced peripheral neuropathies, as indexed by electromyography, assessment of nerve conduction velocity, and observation of other overt neurological signs, such as tremor and wrist or foot drop. Frank neuropathic effects have been observed at PbB levels of 60 to 80 μg/dl (Erenberg *et al.*, 1974). In one case study

(Seto and Freeman, 1964), signs indicative of peripheral neuropathy were reported to be associated with PbB values of 30 μg/dl; however, lead lines in long bones suggested probable past exposures leading to peak PbB levels at least as high as 40 to 60 μg/dl and probably in excess of 60 μg/dl (based on the data of Betts *et al.*, 1973). In all these case studies, some, if not complete, recovery of affected motor functions was reported after treatment for lead poisoning. A tentative association has also been hypothesized between sickle cell disease and increased risk of peripheral neuropathy as a consequence of childhood lead exposure. Half of the cases reported (10 out of 20) involved inner-city black children, several with sickle cell anaemia (Anku and Harris, 1974; Lampert and Schochet, 1968; Seto and Freeman, 1964; Imbus *et al.*, 1978). In summary, evidence exists for frank peripheral neuropathy in children, and such neuropathy can be associated with PbB levels at least as low as 60 μg/dl and, possibly, as low as 40 to 60 μg/dl.

Further evidence for lead-induced peripheral nerve dysfunction in children is provided by two studies by Feldman *et al.* (1973a,b, 1977) of inner city children and from a study by Landrigan *et al.* (1976) of children living close to a smelter in Idaho. No clearly abnormal conduction velocities were observed, although a statistically significant negative correlation was found between peroneal NCV and PbB levels ($r = -0.38$, $p < 0.02$ by one-tailed t-test). These results, therefore, provide evidence for significant slowing of nerve conduction velocity (and, presumably, for advancing peripheral neuropathy as a function of increased PbB levels), but do not allow clear statements regarding a threshold for pathological slowing of NCV.

In a recent study mentioned earlier, Winneke *et al.* (1984) evaluated neurophysiological functions as well as neuropsychological performance in children from Nordenham, FRG. Results from a standard neurological examination and sensory nerve conduction velocities of the radial and median nerves were analysed in relation to concurrent PbB values and umbilical cord PbB levels sampled approximately six years earlier. Contrary to expectations, increasing conduction velocities for radial and median nerves were found to be significantly associated with current PbB levels (at $p < 0.01$ and < 0.10, respectively). As noted above, visual evoked potentials showed a significantly decreased latency in one component, which suggested more rapid conduction in the visual pathway, consistent with the peripheral nerve conduction findings. Somatosensory evoked potentials showed no significant effect; nor were associations found between any of the electrophysiological measures and cord PbB levels or any of a number of socio-hereditary background variables (the latter of which were strongly related to neuropsychologic outcome results).

The lead-associated increases in nerve conduction observed by Winneke *et al.* (1984) for children with PbB levels below 25 to 30 μg/dl differ from previously noted findings of slowed NCVs being associated with increasing PbB values above 30 μg/dl. However, the apparently paradoxical findings were noted by the investigators as being consistent with those of Englert (1978), who similarly found an increase in the motor NCV of the median nerve among lead-exposed children in Nordenham. Davis and Svendsgaard (1987a) have discussed these and other examples of 'U-shaped' dose–response

relationships for lead as well as other toxic agents. However, as Winneke *et al.* (1984) have noted, these findings still require experimental confirmation before a bi-phasic effect of lead on peripheral nervous functions can be assumed. See additional discussion of these results and related findings by Winneke and colleagues elsewhere in these proceedings.

EFFECTS OF LOW-LEVEL LEAD EXPOSURE ON EARLY DEVELOPMENT

Prospective studies of human populations

That lead can affect the survival and development of the fetus and infant has been known since at least the 1800s (Paul, 1860). Indeed, around the turn of the century, lead was routinely sold as an abortifacient (Hall and Cantab, 1905). Studies of experimental animals have also amply demonstrated lead's gametotoxic, embryotoxic, and teratogenic properties (US EPA, 1986a). Most of this evidence, however, has involved relatively high levels of exposure, at least by today's standards, and may have been confounded by factors such as nutritional deficits. Also, the relevance of findings from animal studies, e.g., malformations in chicks (Gilani, 1973a,b), is not always clear. Some studies have pointed to a number of effects in humans at ambient exposure levels, including decreased birth weight, shortened gestation, and stillbirths (Fahim *et al.*, 1976; Nordstrom *et al.*, 1979; Khera *et al.*, 1980). But other investigations have not supported these findings (Clark, 1977; Alexander and Delves, 1981; Roels *et al.*, 1978).

One of the difficulties in drawing conclusions from many of the past studies of the reproductive and developmental effects of lead derived from problems in accurately measuring PbB levels (see Chapter 9, US EPA, 1986a). In addition, the statistical power of earlier studies was often limited by the small number of subjects employed. In recent years there have been notable improvements in the design and methodology of studies of lead effects. These improvements owe a great deal to the exchange of information among investigators in this area of research and the careful examination of their results by one another and by other 'interested parties', such as scientists for government agencies or other organizations with a direct interest in the implications of this work. Meetings such as the present international workshop and past conferences (e.g., Bornschein and Rabinowitz, 1985) have contributed to these beneficial interactions among scientists.

Although cross-sectional epidemiological studies, particularly those discussed earlier in this paper and elsewhere in this volume, provide important information on the health effects of environmental lead exposure, the emergence of prospective studies of lead's developmental effects has offered a notable advantage over the cross-sectional approach, namely a more precise characterization of the history of lead exposure during the period of development. The primary focus here is therefore on emerging prospective investigations of the relationship between lead and early development.

Although it may go without saying that early human development is

influenced by many variables, early studies of lead's effects did not always succeed in dealing with these 'extraneous' factors. The studies to be discussed here have taken into consideration an impressive number of such variables as potential covariates or confounders of a relationship between lead and developmental outcomes. In general, current studies demonstrate a high degree of sophistication in design, methodology, and data analysis.

Of the several prospective studies currently under way in various parts of the world, three in the United States – in Boston, Cincinnati, and Cleveland – and one in Port Pirie, South Australia have progressed far enough to provide published findings for the purposes of this review. Since these studies are already quite well represented by other papers in this volume and have been discussed in greater detail in US EPA (1986b) and by Davis and Svendsgaard (1987b), only the major features of these studies are summarized here. Attention is devoted primarily to the convergences in these studies and to their collective implications for public health. Additional information on other prospective studies not yet fully underway or complete in data collection and analysis is also provided elsewhere in this volume (see Graziano *et al.*, McBride *et al.*, Moore *et al.*, and Rothenberg *et al.*).

Table 2 summarizes some of the main features of the study populations for each of the four prospective studies to be examined here. Note that the study populations are generally adequate in size, with *n*'s numbering in the hundreds. However, the actual number of subjects used in specific analyses may be somewhat less than the enrolled population. For the most part, prenatal lead exposure was indicated by the maternal PbB level prior to or at delivery, or cord PbB level at delivery. Note that these average PbB levels were all below 15 μg/dl and are probably representative of past and/or still prevalent levels in various parts of the world.

The studies to be reviewed here have independently assessed many of the same endpoints of physical and/or neurobehavioural development. For example, gestational age, birth weight, and postnatal neurobehavioural development were commonly evaluated. One of the strengths of these studies

Table 2 Summary of population characteristics of prospective lead studies

Location	*n**	*Exposure indicator***	*Mean blood lead* (range), μg/dl	*Reference*
Boston	249	Cord	6.5 (0–25)	Bellinger *et al.* (1984a, 1986a, 1987)
Cincinnati	305	Maternal-pre	8.0 (1–27)	Dietrich *et al.* (1986, 1987b)
		Neonatal	4.5 (1–28)	
Cleveland	359	Maternal-del	6.5 (2.7–11.8)	Ernhart *et al.* (1986, 1987)
		Cord	5.8 (2.6–14.7)	
Port Pirie	831	Maternal-del	11 (?)	McMichael *et al.* (1986); Vimpani *et al.* (1985)
		Cord	10 (?)	
		6-mo	~14 (?)	

*Actual number of subjects used for specific analyses may be somewhat less than number enrolled in study.
**Maternal blood lead measured at delivery (del) or at prenatal clinic visit (pre).

is their use of comparable or even the same assessment techniques. In particular, all four prospective studies used the Bayley Scales of Infant Development, particularly the Mental Development Index, to measure postnatal neurobehavioural development. The Bayley Scales comprise three indices of mental, motor, and emotional development. Of the three, the Mental Development Index (MDI) has the greatest reliability and validity, and was designed to assess: "senory-perceptual acuities, discriminations, and the ability to respond to these; the early acquisition of 'object constancy' and memory, learning, and problem-solving ability; vocalizations and the beginnings of verbal communication; and early evidence of the ability to form generalizations and classifications, which is the basis of abstract thinking" (Bayley, 1969).

Table 3 summarizes the neurobehavioural results from the prospective studies. Note that the magnitude of the deficit in Bayley MDI scores is fairly consistent across studies: about 2 to 8 points per 10-μg/dl increase in blood lead level. Also to be noted are the lowest-observed-effect levels (LOELs) for these effects. Since each study deals with data in a slightly different way, the studies will be discussed individually to explain how the information in Table 3 was derived.

In the case of the Boston study (Bellinger *et al.*, 1987), a difference of 4 to 8 points, after control for potential confounders, between low (mean = 1.8 μg/dl) and high (mean = 14.6) cord PbB groups has been found at 6-month intervals over the first two years of life. Since the deficit in the high-exposure group was evenly distributed throughout that group (that is, the decrease in MDI scores was not associated primarily with the subjects having the highest PbB levels), it appears that the effect occurred at PbB levels as low as 10 μg/dl (range for the high-exposure group was 10 to 25 μg/dl).

Somewhat different approaches were used in analysing and reporting the neurobehavioural results from the other prospective studies. Instead of grouping subjects into different levels of exposure, regression analyses were applied to data across the entire range of PbB levels. This approach does not identify a 'threshold' at which effects occur, but it does provide a useful estimate of the quantitative relationship between PbB levels and changes (in this case, decrements) in Bayley MDI scores. Recent results from the Cincinnati study indicate, for example, that 6-month-old male infants show an 8-point decrease in the MDI for every 10-μg/dl increase in PbB level (Dietrich *et al.*, 1987b). Separate analyses of the Cincinnati data led Bornschein *et al.* (this volume) to conclude that a threshold for reductions in birth weight related to prenatal lead exposure existed at about 12 to 13 μg/dl. Since structural equation models indicated that birth weight mediated, at least in part, the effect of prenatal lead exposure on MDI, by inference one could conclude that the MDI effect had the same threshold. As a rough estimate, then, 12 to 13 μg/dl PbB can be taken as the LOEL for MDI effects in the Cincinnati study.

Table 3 Summary of neurobehavioural findings from prospective lead studies

Study	*MDI deficit pts.*	*Average PbB* (range), μg/dl
Boston	4 to 8*	14.6 (10–25)
Cincinnati	8	~12.5 (7–18)
Cleveland	?	? (3–15)
Port Pirie	2	~14 (?)

*Differences between high- and low-exposure groups in Boston at 6-month intervals during first 2 years; other studies report deficit per 10-μg/dl increment in blood lead level.

Reported analyses of the Cleveland data have not provided information on either the magnitude of the lead effect or the level at which it occurs. Indeed, Ernhart *et al.* (1986, 1987) have repeatedly concluded that their data show no clear indication of an effect of low-level lead exposure on fetal or child development. Nevertheless, results from the Cleveland study show some consistency with findings from the other prospective studies. Assessment of neonatal neurobehavioural function indicated that scores on the Graham–Rosenblith Neurological Soft Signs Scale were significantly related to cord PbB levels, even after reducing the data set to only 132 cases. While this single result in itself does "not provide a reasonable level of support for the hypothesis of adverse effects due to intrauterine low-level lead exposure", as Ernhart *et al.* (1986) said, it does provide an intriguing link to another finding from the Cleveland study. Wolf *et al.* (1985) reported that the 12-month MDI scores of subjects from this study were significantly related to Neurological Soft Signs scores shortly after birth. Thus, one could infer that prenatal lead exposure (as reflected in cord PbB level) is associated, indirectly, with performance on the Bayley MDI at 12 months of age. The Cleveland investigators are properly cautious about interpreting these specific results from their study, but in the larger context provided by the other prospective studies these findings are entirely consistent with and supportive of the conclusion that intrauterine lead exposure results in impaired postnatal neurobehavioural development. Moreover, the comparatively low levels of exposure (mean PbB ~6 μg/dl) and reduced number of subjects actually used in the analyses (n = 132), suggest that the effect would have had to be fairly robust to be detected at all in the Cleveland study. The fact that the highest individual PbB level in this study was only 14.7 μg/dl necessarily implies that the LOEL had to be below 15 μg/dl, and could have even been below 10 μg/dl.

The Port Pirie study also demonstrates an effect of lead exposure on the Bayley MDI. In this case, the MDI was administered only at 2 years of age, but PbB measurements were taken at various points starting with the mother during pregnancy and from birth onward in the infants. The only PbB measurement to show a significant relationship to 24-month MDI performance, after correcting for covariates such as maternal intelligence and HOME scores, was the 6-month postnatal PbB level. The first report of this finding indicated that for an increase of 10 μg/dl in mean blood lead level, there was a 4-point decline in MDI performance (Vimpani *et al.*, 1985). More recent analyses (Vimpani *et al.*, this volume) suggest that the decrease in MDI scores may be closer to two points. While the magnitude of deficit is consistent with other findings, the contrast between prenatal and postnatal exposure indicators

in the Port Pirie study does seem at odds with the other studies. However, it should be noted that a clearcut relationship between prenatal lead exposure and pregnancy outcome (in particular, risk of pre-term delivery) was in fact found in this same cohort (McMichael *et al.*, 1986). These findings will be discussed in greater detail below. For now, it is enough to point out that prenatal exposure did have a significant effect on fetal development at mean PbB levels above 14 μg/dl (and possibly starting at somewhat lower levels). By the time of testing on the Bayley MDI at 24 months of age, however, PbB levels had risen to approximately 21 μg/dl. It seems plausible that earlier testing on the Bayley MDI, i.e., before the rather precipitous increase in PbB levels between birth and 24 months, might have revealed a relationship between prenatal exposure indicators and MDI performance that was no longer detectable at 24 months.

Some of the other developmental effects that have been revealed in the prospective studies are summarized in Table 4. The duration of gestation is reduced as a function of lead exposure in two of these studies. In the Port Pirie study (McMichael *et al.*, 1986), this effect was reflected in a categorical measure, pre-term delivery (i.e., before the 37th week of pregnancy). The relative risk of pre-term delivery was noted to increase 2.8-fold for every 10-μg/dl increase in maternal PbB levels. Alternatively, at PbB levels above 14 μg/dl, the risk of pre-term delivery was 4.4 times that at 8 μg/dl or below. When late fetal deaths were excluded, the risk was even greater: an 8.7-fold increase in relative risk. These findings indicate that the effect occurred at PbB levels at least as low as 15 μg/dl.

The Cincinnati study also has found an effect of prenatal lead exposure on gestational age, measured in weeks as a continuous variable. One analysis (Dietrich *et al.*, 1986) indicated that gestational age was reduced by approximately 0.6 week for each natural log unit of prenatal maternal blood lead (PbB measurements were transformed to natural logarithms for these analyses to better approximate a normal distribution). Also related to these findings is the cross-sectional study by Moore *et al.* (1982), which has shown a significant relationship between pre-term delivery and either maternal or cord PbB levels in Glasgow, Scotland. This relationship held even after adjustment for a number of possible confounders.

Fetal growth also appears to be affected. Head circumference was reduced approximately 0.3 cm for every 10 μg/dl of blood lead in Port Pirie mothers

Table 4 Summary of other developmental findings related to lead exposure

Study	*Effects*	*Magnitude of effects*[a]
Port Pirie	Pre-term delivery	2.8 × Rel. Risk
	Head circumference	−0.3 cm
Cincinnati	Gestational age	−0.6 wk
	Birth weight	−225 g
	Birth length	−2.5 cm

[a]Per 10-μg/dl increment in PbB in Port Pirie; per natural log unit PbB in Cincinnati.

(McMichael *et al.*, 1986). Birth weight and length were also significantly reduced in Cincinnati infants (Dietrich *et al.*, 1986; Bornschein *et al.*, this volume), although the effect on length was evident only in white infants.

A variety of other findings related to fetal development and growth have been provided by the prospective studies, but are perhaps less clearcut. These findings have been discussed in greater detail by US EPA (1986b) and Davis and Svendsgaard (1987b).

The evidence summarized in this section is remarkably consistent in indicating that exposure to lead during early development is linked to disturbances in fetal and postnatal development. Specifically, these studies indicate statistically significant deficits of 2 to 8 points on the Bayley Mental Development Index for every 10-μg/dl increase in PbB level. In addition, gestational age, birth weight, and possibly other aspects of fetal growth and development appear to be reduced by prenatal lead exposure. Taken collectively, the evidence suggests that PbB concentrations of 10 to 15 μg/dl, and possibly even lower, constitute a level of concern for developmental deficits arising from early lead exposure. Note that this level of concern has heretofore been considered well within the safe or even 'normal' range of PbB values.

Given these conclusions, the obvious question is, "What are the implications for the public health?" First, what portion of the population is at risk? Based on data from the National Center for Health Statistics (1982), approximately 3.6 million live births occurred in the United States in 1980. Data from the US National Health and Nutrition Examination Survey for about the same period (February 1979 to February 1980) indicate that about 27% of the women of child-bearing age had PbB concentrations of 10 μg/dl or more (*cf.* Schwartz *et al.*, 1985). Thus, nearly 1 million infants may have been born in the United States around 1980 to mothers with maternal PbB levels high enough to put the infants at risk for developmental impairments. Blood lead levels in the United States have probably declined somewhat since then due to reduced ambient levels (Schwartz *et al.*, 1985), but the scope of potential concern is still significant, particularly in parts of the world where ambient levels may be greater.

In assessing the public health significance of the above findings, one may also ask what is the significance of a 2- to 8-point decline on the Bayley Mental Development Index? The Bayley MDI has been the most reliable and valid indicator available for assessing the current state of an infant's development (Honzik, 1977). Although its ability to predict later cognitive or intellectual function has been debated (Wilson, 1973; Lewis and McGurk, 1973), the MDI generally shows moderate, positive, and statistically significant correlations with later childhood IQ test scores (e.g., Wilson and Harpring, 1972). At this time, however, it is impossible to say to what extent later academic, cognitive, or other neurobehavioural performance might be affected by early lead exposure, based on deficits in 6- to 12-month Bayley MDI scores. Clearly, though, such deficits in themselves cannot be assumed to be inconsequential. It is also important to note that these changes represent *average* decrements. Thus, for a population of children, a 4-point downward shift in a normal distribution of MDI scores would result in 50% more children

scoring below 80 (*cf.* Needleman, 1983). Although a 4-point change in an individual child would not generally be considered clinically important, such an effect on a population basis should not be ignored.

Similar considerations apply to the findings on gestational age and fetal growth. In general, reductions in fetal growth are a major risk factor in perinatal morbidity (Yerushalmy, 1970; Usher and McLean, 1974). Moreover, as the work of Dietrich *et al.* (1986, 1987a) has shown, even slight reductions in duration of gestation and birth weight are related to declines in MDI performance. Some recent work also finds a positive relationship between children's height and intelligence (Wilson *et al.*, 1986), which would also suggest that lead-induced effects on growth may have broader health implications.

Lead effects on physical growth/development and their interrelationships with delayed neurobehavioural development have only recently begun to be recognized as being of likely concern at low levels of lead exposure. Among the earliest indications of lead effects on stature in children are observations reported by Nye (1929) regarding 'runting', along with squint and foot drop, as physical signs characteristic of overtly lead-poisoned Australian children seen in the 1920s. Remarkably, since then relatively few systematic evaluations of possible stunting of physical growth have been included among the health endpoints examined in the numerous epidemiological studies of lead effects on early human development. With regard to such studies, some have provided suggestive evidence of associations between relative decreases in height and PbB levels in the range of 30 to 80 μg/dl in comparison to 'low-lead' groups (PbB range = 10–30 μg/dl) from among children aged 1–6 y (Mooty *et al.*, 1975; Johnson and Tenuta, 1979; Routh *et al.*, 1979). However, given certain differences in racial composition and mean age of the control and comparison groups in these studies they do not allow clear determination of the relative contribution of lead to the observed smaller stature of the high-lead subjects.

Much stronger evidence for lead exposure producing retardation of growth and decreased stature has more recently emerged in the 1980s from both animal toxicology studies and evaluation of larger scale epidemiological data sets. In regard to the latter, work by Lauwers *et al.* (1986) in Belgium points to associations between lead exposure and disturbed physical growth in young children. Biometric measurements made on 312 children (aged 2.5 to 16 years) included stature, weight, total arm length, biacromial and bicristal diameter, upper arm circumference, thigh circumference, head length and breadth, and bizygomatic diameter; PbB levels were measured an average of 9.5 months earlier and SES was ranked by parental occupation. Univariate and multivariate analyses indicated that low-PbB (0 to 30 μg/dl) and high-PbB (40 to 60 μg/dl) children were significantly different in their biometric profiles. These differences were greatest in children below 8 years of age. Although few specific measures differed significantly between high- and low-PbB groups, the overall differences in profiles are consistent with findings from other studies described above. Also, Schwartz *et al.* (1986) have reported results of analyses of data from the large scale National Health and Nutrition Evaluation Survey (NHANES II) conducted in the United States during 1976–

1980. More specifically, results for anthropometric measurements, as well as numerous other factors (age, race, sex, dietary, etc.) likely to affect rates of growth and development, among the NHANES II children were analysed. Linear regressions of adjusted data from 2695 children (aged 7 y or younger) indicated that 9% of the variance in height, 72% of the variance in weight, and 58% of the variance in chest circumference were explained by the following six variables: age, race, sex, blood lead, total calories or protein, and haematocrit or transferrin saturation. The step-wise multiple regression analyses further indicated that PbB levels were a statistically significant predictor of children's height ($p < 0.0001$), weight ($p < 0.001$), and chest circumference ($p < 0.026$), after controlling for age (in months), race, sex, and nutritional covariates. The strongest relationship was found between PbB and height, with threshold regressions indicating no evident threshold for the relationship down to the lowest observed blood lead level of 4 μg/dl. At their average age (59 mo.), the mean PbB level of the children appears to be associated with a reduction of about 1.5% below the height expected if their PbB level had been zero, and the relative impacts on weight and chest circumference were of the same magnitude. Overall, these findings appear to be highly credible, being based on well-conducted statistical analyses of a large-scale national survey data set that was subjected to rigorous quality assurance procedures and took into account numerous potentially confounding variables.

Although the full ramifications of early developmental impairments due to lead cannot be stated at present, the *prima facie* indications are that such effects should be avoided. One factor to be considered in evaluating the public health implications of these findings is their relative permanence or irreversibility. Broadly speaking, ontogeny is characterized both by plasticity and by sequential dependency. Developing organisms are often able to compensate for deficiencies, even major neurological impairments, if they occur early enough in the maturation of the individual. Catch-up growth spurts in children are a well-known example of such compensatory phenomena (Ashworth and Millward, 1986). Thus, one might suppose that early developmental lags, particularly those that are fairly subtle (as suggested by the findings reviewed here), could 'disappear' at later ages.

On the other hand, even if a lead-induced lag in cognitive or physical development were no longer *detectable* at a later age, this would not necessarily imply that the earlier impairment was without consequence. Decades of research in developmental psychology have affirmed and extended the early work of Carmichael (1926, 1927), who showed that the actualization of behavioural capabilities as basic as a tadpole's swimming movements requires appropriate periods of functional neural activity for proper development. Of more immediate relevance, perhaps, is recent work on the subtle impairments of language acquisition in children whose hearing has been affected by intermittent otitis media (e.g., Needleman, 1977). Although much remains to be learned about this particular issue, it illustrates the potential for serious and long-lasting sequelae of deficits that may be only transient and, in themselves, reversible during early development. Moreover, secondary effects of early developmental perturbations need not be strictly sequential. Given

the complex interactions that figure in the cognitive, emotional, and social development of children, it could well be that attempts to compensate for lead-induced deficits in one area of a child's development may exact a cost in another area of development. Thus, even if lead-induced deficits on the Bayley scales do not eventually predict other specific deficits, such as reduced IQ test performance in later childhood, one needs to be careful in assessing the full and ultimate cost to the developing child, and hence the public health.

Continued research is obviously needed to determine the ultimate impact of early developmental lead exposure. Such work needs to follow current cohorts of subjects with appropriate assessments of cognitive, emotional, social, and physical development. In addition, interactive effects involving variables such as socioeconomic status (Bellinger *et al.*, this volume), gender (Dietrich *et al.*, 1986), and race (Dietrich *et al.*, this volume) need to be investigated. Much remains to be learned about the critical periods during development for the induction of lead's effects and the levels of exposure responsible for these effects. Estimating fetal lead exposure from maternal or cord PbB levels, for example, is far from precise. More accurate indicators of fetal exposure are needed if early developmental effects are to be detected reliably. In addition, the possible contribution of paternal lead exposure to these effects needs to be investigated (*cf.* Uzych, 1985; Cohen, 1986). The findings reviewed here provide more than adequate impetus for pursuing these questions.

INTERPRETIVE SUMMARY AND EVALUATION

Assessment of the impact of lead on human physical and neurobehavioural development raises a number of issues. Among the key points addressed here are the following: (1) the internal lead exposure levels, as indexed by PbB levels, at which various effects on physical and neurobehavioural development occur; (2) the reversibility of such deleterious effects; and (3) the populations that appear to be most susceptible to neural damage. In addition, note is made that animal toxicology studies provide parallels to the human study results.

Internal exposure levels associated with effects on neurobehavioural development

Markedly elevated PbB levels are associated with readily detectable neurotoxic effects (including severe, irreversible brain damage as indexed by the occurrence of acute and/or chronic encephalopathic symptoms) in both humans and animals. For most adult humans, such damage typically does not occur until PbB levels exceed 100 to 120 μg/dl. In children, effective PbB levels for producing encephalopathy or death are somewhat lower, encephalopathy signs and symptoms having been reported for some children at PbB levels as low as 80 to 100 μg/dl. In addition, numerous studies show that children with high blood lead levels (over 80 to 100 mg/dl), but not

observed to manifest acute encephalopathic symptoms, are permanently cognitively impaired, as are most children who survive acute episodes of frank lead encephalopathy.

Other evidence reviewed here confirms that various types of neural dysfunction also exist in apparently asymptomatic children across a broad range of PbB levels. The body of studies on low- or moderate-level lead effects on neurobehavioural functions, as summarized in Table 1, presents a rather impressive array of data pointing to that conclusion. It is true that numerous types of methodological problems or weaknesses are associated with many of the studies in Table 1. Such problems, at times, limit acceptance of their resulting published findings or conclusions and make overall interpretation of their results difficult. However, careful examination of the studies both individually, weighing specific limitations against other (sometimes offsetting) considerations, and collectively nevertheless yields useful information on the effects of lead on neurobehavioural functions in non-overtly lead-intoxicated children.

Figure 1, for example, illustrates the general pattern that seems to emerge from most of the available studies in terms of the magnitude of lead effects on one commonly employed measure of children's mental abilities, i.e., full-scale IQ. Clearly, many caveats are in order in regard to the interpretation presented in Figure 1. First, 'IQ' was measured by many different specific test instruments across the various studies reviewed earlier and those upon which the figure is based. The tests, especially their subscales, may be tapping different specific abilities and, thus, it could be argued that no quantitative comparison across studies can be made. On the other hand, full-scale IQ scores derived from various test instruments, overall, generally tend to reflect roughly similar constellations of mental capabilities and some reasonable, albeit crude, comparisons should be warranted across various studies. Secondly, the magnitudes of the IQ decrements shown in Figure 1 at different PbB levels are based on the study results reflecting varying degrees of corrections for potentially confounding variables. Some, for example, do not reflect correction for parental IQ whereas others do. Still, the overall pattern of results is revealing.

For comparison's sake, the magnitude of IQ decrements observed by Rummo for postencephalic children is also included, that being about 16 points at mean PbB levels in the range of 80 to 100 μg/dl. At somewhat lower exposure levels, several studies (e.g., Rummo; de la Burde) point to average 5-point IQ decrements in asymptomatic children at average PbB levels in the range of 50 to 70 μg/dl. Other evidence from Needleman's studies is indicative of average IQ decrements of up to 4 points being associated with PbB levels in a 30 to 50 μg/dl range. Below 30 μg/dl, the evidence for IQ decrements has been relatively mixed, with most of the recent British and Winneke's studies showing no statistically significant associations with lead once other confounding factors are controlled. Still, the 1 to 2 point differences in IQ often reported for PbB levels in the 15 to 30 μg/dl range are suggestive of small lead effects that are dwarfed or, quite possibly, masked by other social factors. The complex interrelationships between lead exposure and confounding variables (e.g., lower parental IQ,

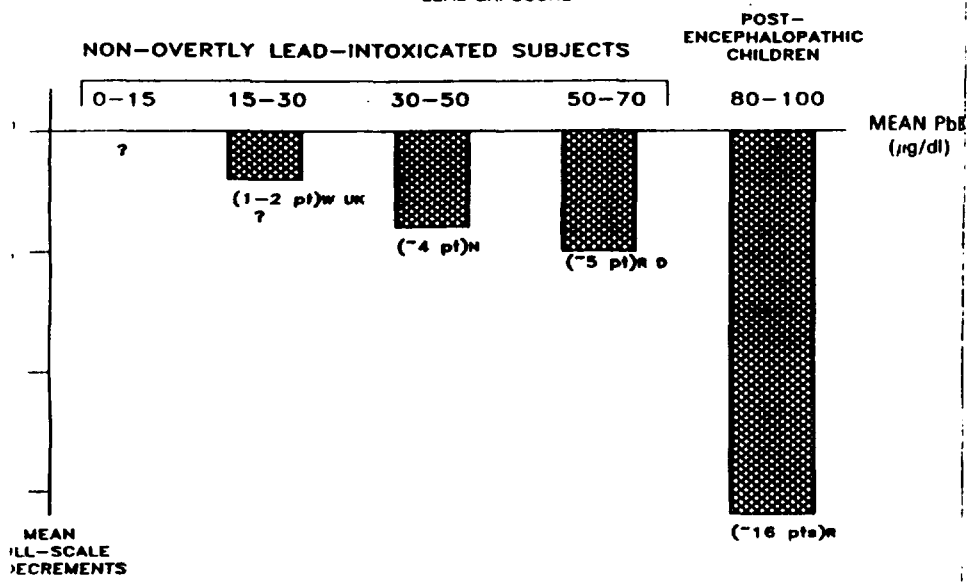

Figure 1 General pattern of results from clinic, smelter, and general population studies of lead exposure effects on cognitive function, as reflected by deficits in IQ scores on various standardized tests. The magnitude of IQ decrements associated with a broad range of blood lead levels is estimated here based on evaluation of studies noted in figure key and discussed in text. Note that latest results from certain newer studies point toward lead effects on IQ across a broad range of PbB levels, down to as low as 10–15 μg/dl or perhaps lower (as illustrated in Figure 2). *Key*: R = Rummo studies; D = de la Burde studies; N = Needleman studies; W = Winneke studies; UK = Recent British studies by Smith, Lansdown, Yule, Harvey, etc.

poorer HOME situations and/or socioeconomic status) complicates conceptual modelling and statistical evaluation of lead effects.

Some investigators, in fact, argue that 'overcorrection' for many confounding factors, which may themselves reflect the impact of lead, tends to lead to underestimation of the magnitude of lead effects. Of interest in that regard are the findings of Schroeder and Hawk (1987) and Fulton *et al.* (1987) plotted

in Figure 2*. The Schroeder and Hawk (1987) finding of a highly statistically significant linear relationship between IQ and PbB over the range of 6 to 47 μg/dl found in uniformly low-SES black children indicates that notable IQ effects may be detected without evident threshold even at these low levels, at least in this population of children where variation in SES levels does not confound the lead effects. Results from the Fulton *et al.* (1987) study described elsewhere in this volume are also plotted in Figure 2. Their results indicate a 5–6 point decrement in British Ability Scale composite and reading attainment scores as average PbB levels increased from 5.6 to 22.1 μg/dl. In addition, other behavioural (e.g., reaction time, psychomotor performance) and electrophysiological (altered EEG patterns, evoked potential measures, and peripheral nerve conduction velocities) effects are consistent with a dose–response function relating neurotoxic effects to lead exposure levels as low as 15 to 30 μg/dl and possibly lower. Also, although the comparability of PbB concentrations across species is uncertain, animal studies (such as those of Rice and Cory-Schlecta reported elsewhere in these proceedings) show neurobehavioural effects in rats and monkeys at maximal PbB levels below 20 to 30 μg/dl.

The medical or health significance of neuropsychological and electrophysiological effects associated with low-level lead exposure as reported in the above studies remains a matter of debate. Observed IQ deficits and other behavioural changes, although statistically significant in some studies, tend to be relatively small as reported by the investigators, but nevertheless may still affect the intellectual development, school performance, and social development of the affected children sufficiently to be regarded as adverse. This would be especially true if such impaired intellectual development or school performance and disrupted social development were reflective of persisting, long-term effects of low-level lead exposure in early childhood.

The question of irreversibility

Relatively little research on children is available on persistence of effects. However, although the issue of persistence of such lead effects remains to be

*Figure 2 presents regression lines relating PbB levels and covariate-adjusted scores from the studies of Schroeder and Hawk (1987) and Fulton *et al.* (1987). The lines were derived from information provided in the original reports as follows. The β coefficient (−0.396) for the sixth model in Table 7 from Schroeder and Hawk (1987) was used to generate a line that passes through the mean average PbB (20.65 μg/dl) and the average Stanford–Binet IQ score (estimated as 87) for that study. Fulton *et al.* (1987) reported a regression coefficient of −3.70 for the relationship between log-transformed PbB levels and adjusted British Ability Scale Composite (BASC) scores in the 'optimum model' in Table III of their report. A curve was therefore constructed to represent this relationship for arithmetic blood lead values to provide comparability to the results of Schroeder and Hawk. The curve was constructed by passing a line through the geometric mean blood lead level (11.5 μg/dl) and the overall mean BASC score (112) in the Fulton *et al.* study. A straight line fitted to that curve over the observed range of blood lead levels, with an average slope of −0.247, is shown in Figure 2. Although these lines are not based on the raw data, they are reasonable derivations and are consistent in showing a negative relationship between PbB and cognitive performance extending to PbB levels well below 10 μg/dl, even in different populations of children whose performance was assessed by different tests.

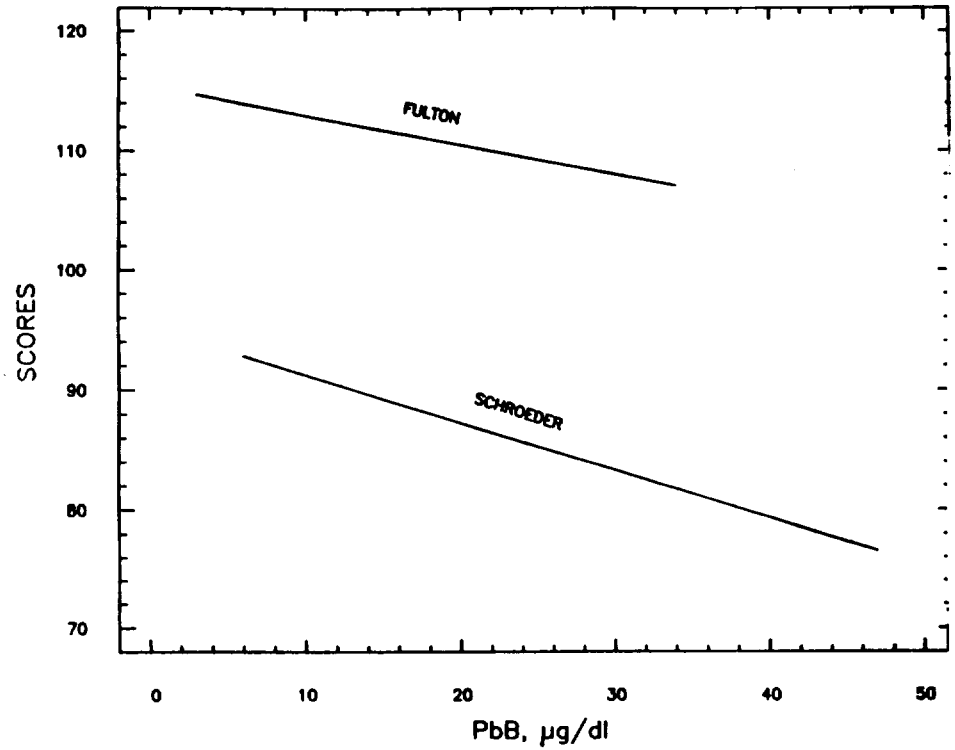

Figure 2 Regression lines relating PbB levels and covariate-adjusted scores for the Stanford-Binet IQ (Schroeder and Hawk, 1987) and the composite British Ability Scale (Fulton *et al.*, 1987). Lines are estimated from the original sources (see discussion in footnote to text)

more clearly resolved, some study results reviewed above suggest that significant low-level lead-induced neurobehavioural and electrophysiological effects may, in fact, persist at least into later childhood. Results from the longitudinal study in Boston indicate a persistent effect of prenatal lead exposure (cord PbB) on postnatal neurobehavioural development (Bayley MDI scores) up to at least 24 months of age. Similarly, the Cincinnati study has thus far observed comparable effects up to 12 months of age. It remains to be seen how long the effects of prenatal lead exposure can be detected in these cohorts at later ages.

The series of studies by Otto and colleagues on a group of lead-exposed children also indicate persistent relationships between PbB and altered electrophysiological responses, e.g., slow wave cortical potentials at two- and five-year follow-ups. However, IQ deficits in the same group of subjects were no longer evident at the five-year follow-up. Some work suggests that other measures of classroom performance may be more sensitive indicators of lead-induced effects in other children. Evaluation of school age IQ, classroom

behaviour, and academic performance in prospective longitudinal studies on lead's developmental effects of the type presented at this meeting will likely be needed to answer questions on the persistence or reversibility of neurotoxic effects of early lead exposure.

Various animal studies provide evidence that alterations in neurobehavioural function may be long-lived, with such alterations being evident long after PbB levels have returned to control levels. These persistent effects have been demonstrated in monkeys as well as rats under a variety of learning performance test paradigms.

Early development and susceptibility to prenatal or early postnatal lead exposure effects

On the question of early childhood vulnerability, the neurobehavioural data are consistent with morphological and biochemical studies of the susceptibility of the haeme biosynthetic pathway to perturbation by lead. Various lines of evidence suggest that the order of susceptibility to neurotoxic effects of lead is: young > adult, and female > male. Animal studies also have pointed to the perinatal period of ontogeny as a particularly critical time for a variety of reasons: (1) it is a period of rapid development of the nervous system; (2) it is a period where good nutrition is particularly critical; and (3) it is a period where the caregiver environment is vital to normal development. However, the precise boundaries of a critical period for lead exposure are not yet clear and may vary depending on the species and function or endpoint that is being assessed. One analysis of lead-exposed children suggests that differing effects on cognitive performance may be a function of the different ages at which children are subjected to neurotoxic exposures. Nevertheless, there is general agreement that human infants and toddlers below the age of three years are at special risk because of *in utero* exposure, increased opportunity for exposure because of normal mouthing behaviour of lead-containing objects, and increased rates of lead absorption due to various factors, e.g., iron and calcium deficiencies. The results emerging from long-term prospective studies reviewed earlier in this paper and presented in more detail by the investigators at this meeting also highlight the vulnerability of the human fetus to lead and reinforce the importance of viewing women of childbearing age as being a population group at special risk as well as young children.

Figure 3 provides a schematic depiction of relationships that have been demonstrated or can be hypothesized to exist between prenatal lead exposure, other factors, and the developmental status of infants, based on results emerging from the long-term prospective studies reviewed here. Significant effects of prenatal lead exposure at maternal and neonatal PbB levels in the range of 10 to 20 µg/dl have been reported for several studies in relation to pregnancy outcomes, with increased spontaneous abortions and stillbirths among the effects observed in some and obstetric complications and/or pre-term deliveries in the same or other studies. As for the offspring, reduced birth weight has been reported by several investigators and lower neurological development scores, e.g., on the Bayley MDI and PDI scales, in relation to

maternal or cord PbB levels. These types of effects may be directly due to prenatal lead or, as hypothesized by some investigators, may be mediated indirectly by lead-induced shortening of the gestation period and, hence, gestational age. Whether prenatal lead exposure induces minor physical malformation at the low exposure levels evaluated by the current studies, as suggested by at least one of them, remains to be more clearly established. The other relationships noted generally appear to have been detectable even when taking into account many other potentially confounding variables, e.g., alcohol and tobacco usage, but may also be related to certain other factors, e.g., parental size, not fully accounted for in some studies.

Proper control for various confounding variables remains an issue of much debate among researchers conducting the prospective studies. One viewpoint is to accept lead effects as being demonstrated only if lead measures are

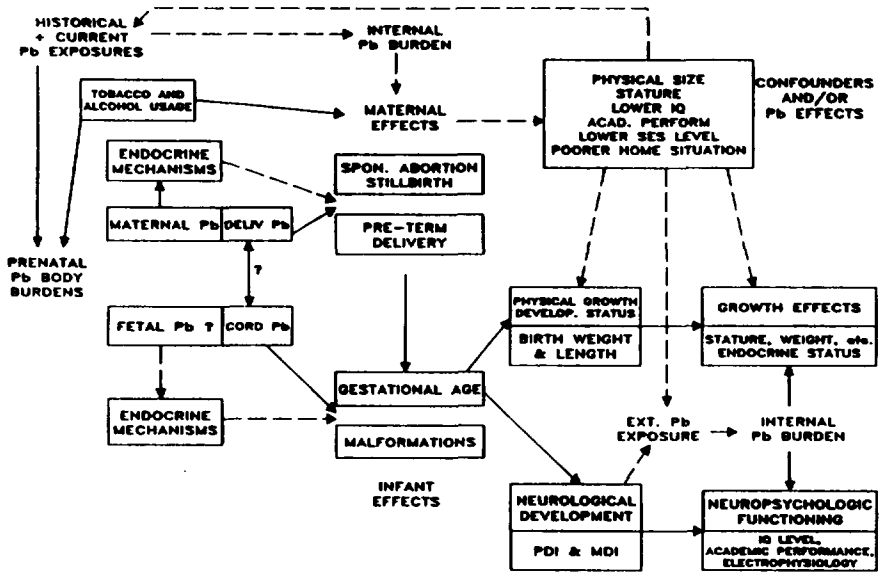

Figure 3 Hypothesized relationships among lead (Pb) and other factors affecting fetal and postnatal development. As discussed in more detail in text, historical and current maternal lead exposures contribute to prenatal lead body burdens, indexed typically by maternal blood lead (PbB) levels during pregnancy or umbilical PbB levels at delivery. Resulting impacts of prenatal exposures include both maternal and infant effects at birth, as well as postnatal effects persisting into later childhood that may be due to the prenatal exposures and/or early postnatal exposures. Potential confounding variables (upper right) make it difficult to quantify precisely effects of lead on dependent variables indicated. An alternative view holds that control for certain confounders may lead to underestimation of lead effects on currently studied subjects, due to 'transgenerational' impacts of lead exposure on the parents of such subjects contributing to negative impacts of the 'confounders' on the lead exposure measures and health effect endpoints

shown to be significantly associated (at $p < 0.05$) with dependent variable outcomes after all possible confounding variables have been accounted for, including variables of the type shown in the upper right of Figure 3. Another viewpoint is that many of the same variables may themselves be determined in part by virtue of past or present lead exposures and, therefore, correction for them may partly obscure otherwise significant lead effects. Also, some of the 'confounders' contribute to increased lead levels in the environment, thus increasing exposure to both parents and children, further complicating separation of the relative contribution of various factors to observed effects.

In addition to highlighting such issues as the above, note should be made of interconnections that may become apparent from diverse areas of investigation reviewed in the present paper. For example, gestational-age-mediated effects on physical size at birth may be related to reduced-stature effects documented for children at later ages and paralleled by observations from animal studies. The earlier discussion of reduced stature effects raises the possibility that neuroendocrine mechanisms underlie effects on postnatal growth or stature: also, attention should be drawn to the possible involvement of prenatal lead effects on endocrine mechanisms in producing both pregnancy outcome effects and/or the observed 'gestational-age' mediated effects on the fetus. Lastly, one might note the possibility of effects of altered neurological development during the early postnatal period resulting in behavioural patterns that may increase lead exposure of the developing child and thereby exacerbate further the effects of earlier prenatal lead exposure.

One other implication of the conceptual scheme in Figure 3 is that early lead exposure of parents may contribute to neurobehavioural and other effects that result in poorer school performance and social behaviour, consequent lower financial or economic success, or other behaviours that place their offspring in more heavily lead-contaminated environments. Their offspring, in turn, may be placed at greater risk for increased lead exposure and continue the experience of their parents, thus manifesting increasingly negative 'transgenerational' effects of lead unless the cycle is broken.

Utility of animal studies in drawing parallels to the human condition

Animal models are used to shed light on questions where it would be impractical or ethically unacceptable to use human subjects. This is particularly true in the case of exposure to environmental toxins such as lead.

Studies using rodents and monkeys have provided a variety of evidence of neurobehavioural alteration induced by lead exposure. In most cases these effects suggest impairment in 'learning', i.e., the process of appropriately modifying one's behaviour in response to information from the environment. Such behaviour involves the ability to receive, process, and remember information in various forms. Some studies indicate behavioural alterations of a more basic type, such as delayed development of certain reflexes. Other evidence suggests changes affecting rather complex behaviour in the form of social interactions. See papers by Rice and by Cory-Schlecta (this volume) for more detailed discussions of such types of effects found in animal

toxicology studies.

Many of the above types of effects are evident in rodents and monkeys with PbB levels exceeding 30 μg/dl, but some effects on learning ability are apparent even at maximum PbB exposure levels below 20 μg/dl. The problem of extrapolating exposures, and therefore the results of animal research to human populations are discussed in another review by Smith (this volume). Until the function describing the relationship of exposure indices in different species is available, the utility of animal models for deriving dose–response functions relevant to humans may be limited. However, consistent observations of altered behaviour across several species and humans at PbB levels below 30 μg/dl tend to converge to indicate lead effects on CNS function at lead levels previously considered 'safe'.

Another neurobehavioural endpoint of interest in comparing human and animal neurotoxicity of lead is electrophysiological function. Alterations of electroencephalographic patterns and cortical slow wave voltage have been reported for lead-exposed children, and various electrophysiological alterations both *in vivo* (e.g., in rat visual evoked response) and *in vitro* (e.g., in frog miniature endplate potentials) have also been noted in laboratory animals. Thus far, however, these lines of work have not converged sufficiently to allow for much in the way of definitive conclusions regarding electrophysiological aspects of lead neurotoxicity.

In addition, lead has been shown to have subcellular effects in the CNS at the level of mitochondrial function and protein synthesis. In particular, some work has indicated that delays seen in cortical synaptogenesis and metabolic maturation following prenatal lead exposure may well underlie the delayed development of exploratory and locomotor function seen in other studies of lead's neurobehavioural effects. Further studies on the correlation between human PbB values and lead-induced disruptions of tetrahydrobiopterin metabolism indicate that subsequent interference with neurotransmitter formation may be linked to small reductions in IQ scores.

Given the difficulties in formulating a comparative basis for internal exposure levels among different species, the primary value of many animal studies, particularly *in vitro* studies, may be in the information they can provide on basic mechanisms involved in lead neurotoxicity. A number of key *in vitro* studies are summarized in US EPA (1986a). These studies show that significant, potentially deleterious, effects on nervous system function occur at *in situ* lead concentrations of 5 μmol/L and possibly lower. This suggests that, at least on an intracellular or molecular level, there may exist essentially no threshold for certain neurochemical effects of lead. The relationship between PbB levels and lead concentrations at extra- or intracellular sites of action, however, remains to be determined.

Despite the problems in generalizing from animals to humans, both the animal and the human studies show considerable internal consistency in that they both support a continuous dose–response functional relationship between lead and neurotoxic biochemical, morphological, electrophysiological, and behavioural effects.

IMPLICATIONS FOR PUBLIC HEALTH PROTECTION

The results of studies reviewed here are very important with regard to their implications for effective actions to protect against health effects associated with lead exposure. These findings should not be viewed in isolation but rather within a context of a wide array of effects associated with exposure of children to lead. It is clear from a wealth of available literature reviewed in Chapter 12 of US EPA (1986a) that there exists a continuum of biological effects associated with lead across a broad range of exposure. At rather low levels of lead exposure, biochemical changes, e.g., disruption of certain enzymatic activities involved in haeme biosynthesis and erythropoietic pyrimidine metabolism, are detectable. Haeme biosynthesis is a generalized process in mammalian species, including humans, with importance for normal physiological functioning of virtually all organ systems. With increasing lead exposure, there are sequentially more intense effects on haeme synthesis as well as a broadening of effects to additional biochemical and physiological mechanisms in various tissues. In addition to haeme biosynthesis impairment at relatively low levels of lead exposure, disruption of normal functioning of the erythropoietic and nervous systems occurs, and additional organ systems are affected, resulting, for example, in manifestation of renal effects, disruption of reproductive functions, and impairment of immunological functions. At sufficiently high levels of exposure, the damage to the nervous system and other effects can be severe enough to result in death or, in some cases of nonfatal lead poisoning, long-lasting sequelae such as permanent mental retardation.

Of particular importance for deriving criteria and developing government policies to protect human health are findings which have bearing on the establishment of quantitative dose–effect or dose–response relationships that can be potentially viewed as adverse health effects likely to occur among the general population at or near existing ambient air exposure levels. Dose–response information for the wide variety of observed lead health effects and their implications for children are discussed in detail elsewhere (US EPA, 1986a). Emphasis is placed on the delineation of internal lead exposure levels, as defined mainly by PbB levels likely associated with the occurrence of such effects. Also discussed are characteristics of these effects that are of crucial importance in determining 'adverse health effects' in human populations.

Over the years, there have been superimposed on the continuum of lead-induced biological effects various judgments as to which specific effects observed in humans constitute 'adverse health effects'. Such judgments involve not only medical consensus regarding the health significance of particular effects and their clinical management, but also incorporate societal value judgments. Such societal value judgments often vary depending upon the specific overall contexts in which they are applied, e.g., in judging permissible exposure levels for occupational versus general population lead exposures. For some lead exposure effects, e.g., severe nervous system damage resulting in death or serious medical sequelae consequent to intense lead exposure, there exists little or no disagreement as to these being significant 'adverse health effects'. For many other effects detectable at sequentially lower levels

of lead exposure, however, the demarcation lines as to what constitutes being 'adverse' and the lead exposure levels at which they reliably occur are neither sharp nor fixed, having changed markedly during the past several decades. That is, from an historical perspective, levels of lead exposure deemed to be acceptable for either occupationally exposed persons or the general population have been steadily revised downward as more sophisticated biomedical techniques have revealed formerly unrecognized biological effects and concern has increased in regard to the medical and societal significance of such effects.

As for dose–response relationships, lowest-observed-effect levels for a variety of important health effects observed in children are discussed in US EPA (1986a). It can be seen there that lead impacts many different organ systems and biochemical/physiological processes across a wide range of exposure levels. These include severe, irreversible CNS damage (manifested in terms of encephalopathic signs and symptoms), permanent severe mental retardation, and other marked neurological deficits among lasting neurological sequelae typically seen in cases of non-fatal childhood lead encephalopathy. Other overt neurological signs and symptoms of subencephalopathic lead intoxication are evident in children at lower PbB levels. Chronic nephropathy, indexed by animoaciduria, is most evident at high exposure levels over 100 μg/dl, but may also exist at lower levels (e.g., 70 or 80 μg/dl). In addition, colic and other overt gastrointestinal symptoms clearly occur at similar or still lower PbB levels in children, at least down to 60 μg/dl. Frank anaemia is also evident by 70 μg/dl, representing an extreme manifestation of the reduced haemoglobin synthesis observed at PbB levels as low as 40 μg/dl, along with other signs of marked inhibition of haeme synthesis at that exposure level. All of these effects are reflective of the widespread marked impact of lead on the normal physiological functioning of many different organ systems, and some are evident in children at PbB levels as low as 40 μg/dl; all of them are widely accepted as being clearly adverse health effects.

Additional studies demonstrate evidence for further, important health effects occurring in non-overtly lead-intoxicated children at similar or lower PbB levels than those indicated above for overt intoxication effects. Among the most important of these are neuropsychological and electrophysiological effects. While the precise medical or health significance of some neuropsychological and electrophysiological effects remain to be more fully defined, IQ deficits and other behavioural changes likely impact the intellectual development, school performance, and social development of the affected children sufficiently to be regarded as adverse. This is especially true if such impaired intellectual development or school performance and disrupted social development are reflective of persisting, long-term effects of low-level lead exposure in early childhood. The issue of persistence of such lead effects still remains to be more clearly resolved, with some study results reviewed above suggesting relatively short-lived or markedly decreasing lead effects on neuropsychological functions from early to later childhood and other studies suggesting that significant low-level lead-induced neurobehavioural and EEG effects may, in fact, persist into later childhood.

Research concerning lead-induced effects on haeme synthesis also provides

information of importance in evaluating what PbB levels are associated with significant health effects in children. As discussed in US EPA (1986a) lead affects haeme synthesis at several points in its metabolic pathway with consequent impact on the normal functioning of many body tissues. Of special interest at low PbB levels are lead effects on haeme synthesis beyond metabolic steps involving ALA. The level of erythrocyte protoporphyrin (EP) in the blood is one commonly employed index of lead exposure used for medical screening purposes. The threshold for elevation of erythrocyte protoporphyrin (EP) levels is well-established as being 25 to 30 μg/dl in adults and approximately 15 μg/dl for young children, with significant EP elevations (>1 to 2 standard deviations above reference normal EP mean levels) occurring in 50% of all children studied as PbB approaches or moderately exceeds 30 μg/dl.

Recently, it has also been shown in children that lead interferes with vitamin D metabolism, with the negative association existing down to 12 μg/dl PbB. This lead effect is of considerable significance on two counts: (1) altered vitamin D metabolism not only impacts calcium homeostasis (affecting mineral metabolism important in bone formation and growth) but also likely impacts calcium's known roles in immunoregulation and tumorigenesis processes; and (2) the effect of lead on vitamin D is a particularly robust one, with PbB levels of 30 to 50 μg/dl resulting in effects that overlap comparable degrees of impairment seen with severe kidney injury or certain genetic diseases.

Also adding to the concern about low level lead exposures are results of an expanding array of animal toxicology studies which demonstrate the following: (1) persistence of lead-induced neurobehavioural alterations well into adulthood long after termination of perinatal lead exposure early in development of several mammalian species; (2) evidence for uptake and retention of lead in neural and non-neuronal elements of the CNS, including long-term persistence in brain tissues after termination of external lead exposure and return to 'normal' PbB levels; and (3) evidence from various *in vivo* and *in vitro* studies indicating that, at least on a subcellular–molecular level, no threshold may exist for certain neurochemical effects of lead.

Given the above new evidence that is now available, indicative of significant lead effects on nervous system functioning and other important physiological processes as PbB levels increase above 10 to 20 μg/dl, the rationale for considering 30 μg/dl as a 'maximum safe' blood lead level, as was the case in setting the 1978 EPA lead National Ambient Air Quality Standards (Federal Register, 1978), is called into question and substantial impetus is provided for revising the criteria level downward. At this time, it is difficult to identify specifically what PbB criteria level would be appropriate in view of the existing medical information. Clearly, however, 30 μg/dl does not afford any margin of safety before reaching PbB levels associated with unacceptable risk of notable adverse health effects in some children. This is based on at least two grounds: (1) blood lead levels in the 30 to 40 μg/dl range are now known to 'mask', for some children, markedly elevated chelatable body lead burdens that are comparable to lead burdens seen in other children displaying overt signs and symptoms of lead intoxication, and (2) PbB levels in the 30

to 40 μg/dl range are also associated with the onset of deleterious effects in several organ systems which are either individually or collectively seen as being adverse. These and other considerations have led the medical community (US Centers for Disease Control, 1985) to define 25 μg/dl PbB as a level associated with unacceptable risk for paediatric lead toxicity and to note that even lower PbB levels should not be taken as 'safe'.

At levels below 25 to 30 μg/dl, many of the different smaller effects reported as being associated with lead exposure might be argued as separately not being of clear medical significance, although each is indicative of interference by lead with normal physiological processes. On the other hand, the collective impact of all of the observed effects (representing potentially impaired functioning and depleted reserve capacities of many different tissues and organs) can, at some point distinctly below 25 to 30 μg/dl, be seen as representing an adverse pattern of effects worthy of avoidance. The onset of signs of detectable haeme synthesis impairment in many different organ systems at PbB levels starting around 10 to 15 μg/dl, along with increasing indications of altered nervous system activity, might be viewed as such a point. The demonstration of significant prenatal or early postnatal lead exposure effects of the type being found by prospective studies of the type reviewed here is increasingly discussed as providing the bases for viewing even lower PbB levels (e.g., 10 to 15 μg/dl or, perhaps, lower) as being associated with unacceptable risk.

FUTURE RESEARCH DIRECTIONS

The extensive and widely varying studies reviewed in the present paper have provided extremely valuable information regarding low level lead effects on the neuropsychological development of children. Still, many issues remain to be resolved and it is useful to highlight some considerations here which may assist in shaping future research in the field.

Findings of recent prospective studies from Boston, Cincinnati, Port Pirie, and Cleveland show consistent declines in Bayley Scales performance and in other aspects of growth and development (gestational age, birth weight, and possibly other outcomes) as a function of low-level lead exposure early in development. Despite the notable methodological advances and convergent results these studies exemplify, further questions arise from this work. Although PbB concentrations appear to be measured reliably and accurately in recent prospective studies, the assessment of 'prenatal lead exposure' requires further elucidation. The fact that different indices of prenatal exposures were used by different research groups is the first sign that matters may be a bit more complex than they appear at first glance. The Boston study obtained only cord blood lead. The Cincinnati study collected cord blood, but used only maternal blood leads obtained at the first prenatal visit (generally first or second trimester) for the initial reported analyses. The Port Pirie study collected maternal blood leads at various points during pregnancy and at delivery, as well as cord blood lead. The Cleveland study used both cord and maternal blood lead at delivery.

All of these studies continued to monitor postnatal exposure through periodic PbB levels of the children. In every study some effect of prenatal exposure was demonstrated, although the effect on Bayley Scales performance in the Port Pirie study was more clearly associated with postnatal rather than prenatal exposure. While the Port Pirie study would appear to be the anomaly in this respect, that study also had the largest study population and the most frequent PbB measurement protocol, facts which make it difficult to disregard its finding in this regard. Of course, there are noteworthy differences among the study populations and their sources of exposure that could underlie this apparent discrepancy. Further study might resolve this matter.

More importantly, even though the preponderance of work shows an effect of prenatal exposure, it is not clear which index of prenatal exposure is the most valid or useful. The basic problem in accurately gauging prenatal lead exposure is that the dynamics of the situation make single determinations of PbB levels a questionable basis for judging the overall level of prenatal exposure. First of all, there may be changes in exposure during the course of gestation that are not adequately reflected in a PbB measurement at delivery (or any other single point in time). In addition, the dynamics of the mother–fetus transfer of lead make it difficult to determine the fetal portion of the shared lead burden. Some evidence from the Port Pirie study as well as other work suggests the possibility that the fetus may serve as a sink for the mother's body burden, at least in some cases. What is needed is a more frequent assessment of mothers during the course of pregnancy and delivery. Such research would be particularly useful to those concerned with the formulation of regulatory standards for lead, as it would help show whether maternal PbB concentrations are an adequate index of fetal lead exposure at the population level.

Another aspect of these prospective studies that bears further investigation is the long-term consequences of demonstrated early developmental effects. Previous basic research has shown that the Bayley Scales, although reliable and valid (particularly for below-average children), are only moderately good at predicting later intelligence measures or academic performance. Thus, the implications of small decreases (approximately 0.4 point on the Bayley MDI for every μg/dl of blood lead) in early development for later cognitive and academic performance are not clear at present. Continued assessment of cognitive, social, and emotional development, along with academic performance, seems advisable as long as any effects are detectable.

Physical growth and stature ought to be included here as well, not only because of findings relating reduced gestational age and birth weight to prenatal lead exposure, but in view of recent analyses (Schwartz *et al.*, 1986; Lauwers *et al.*, 1986) indicating effects on growth associated with PbB levels in children up to 7 or 8 years of age and parallel animal study findings (e.g., Grant *et al.*, 1980) demonstrating effects of prenatal lead exposure on birth weight and length in neonatal rats. Results from the Grant study indicate persisting slower growth rates with continuing postnatal lead exposures. Thus, prospective study researchers may have an unusual opportunity to tease out analogous physical development sequelae that heretofore have largely escaped detection.

Investigators in this field might also wish to consider assessing other endpoints as well. Recent analyses of NHANES data by Schwartz and Otto (1987) suggest that various developmental milestones (age at which a child first sat up, walked, spoke) were related to lead exposure. In addition, hearing thresholds of children were significantly higher as lead exposure increased. The latter finding is particularly noteworthy in view of previous work relating brainstem auditory evoked potentials to low-level lead exposure in children. Investigators might consider assessing these and other electrophysiological endpoints having demonstrated clinical utility. Electrophysiological measures may yet prove to be a useful neurotoxicological assay for detecting lead effects at very low exposure levels.

Not to be forgotten is the question of the mechanisms underlying the developmental deficits thus far demonstrated by prospective epidemiological studies. The interaction of physiological, genetic, socio-cultural, and nutritional factors involved in development and growth makes it very difficult to elucidate lead's role in such effects. This may explain why so little experimental work has been devoted to examining how lead might affect endocrine and other mechanisms related to growth and development. Elucidation of neuroendocrine mechanisms potentially involved in the mediation of perinatal and later lead effects on development would seem to be a particularly promising research direction.

The call to pursue underlying mechanisms raises a more general point related to research needs. As environmental exposure levels of lead continue to decline, there is sometimes a tendency to view lead studies as passé. Having identified a problem and taken major steps to eliminate it (if one may speak so simplistically about lead), we may not see any need to further understand it. Certainly this is an understandable point of view from a regulatory perspective. But from the standpoint of the science of environmental toxicology, it seems shortsighted to fail to follow through on unresolved questions about an environmental pollutant that has probably been investigated more than any other.

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